U.S. DEPARTMENT OF COMMERCE
National Technical Information Service

PB-285 881

Investigation of Selected Potential Environmental Contaminants Acrylonitrile

Franklin Inst Research Labs, Philadelphia, Pa

Prepared for

Environmental Protection Agency, Washington, D C

May 78

PB 285 881

EPA 560/2-78-003

INVESTIGATION OF SELECTED POTENTIAL ENVIRONMENTAL CONTAMINANTS: ACRYLONITRILE

By:

Lynne M. Miller
Jon E. Villaume

May 1978
Final Report
EPA Contract No. 68-01-3893
FIRL No. 80G-C4807-01

Technical Advisor
Dr. Patricia M. Hilgard

Project Officer
Frank J. Letkiewicz

Prepared For:
Office of Toxic Substances
U.S. Environmental Protection Agency
Washington, D.C. 20460

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U. S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

Science Information Services Organization
THE FRANKLIN INSTITUTE RESEARCH LABORATORIES
THE BENJAMIN FRANKLIN PARKWAY • PHILADELPHIA, PENNSYLVANIA 19103

251

TECHNICAL REPORT DATA

(Please read Instructions on the reverse before completing)

1. REPORT NO.
EPA 560/2-78-003

2.

3. RECIPIENT'S ACCESSION NO.
PB285881

4. TITLE AND SUBTITLE
Investigation of Selected Potential Environmental Contaminants: Acrylonitrile

5. REPORT DATE
May 1978

6. PERFORMING ORGANIZATION CODE

7. AUTHOR(S)
Lynne M. Miller and Jon E. Villaume

8. PERFORMING ORGANIZATION REPORT NO.
FIRL 80G-C4807-01

9. PERFORMING ORGANIZATION NAME AND ADDRESS
Science Information Services Organization
Franklin Institute Research Laboratory
20th and Race Streets
Philadelphia, Pa. 19103

10. PROGRAM ELEMENT NO.

11. CONTRACT/GRANT NO.
EPA 68-01-3893

12. SPONSORING AGENCY NAME AND ADDRESS
Office of Toxic Substances
U.S. Environmental Protection Agency
Washington, D.C. 20460

13. TYPE OF REPORT AND PERIOD COVERED
Final Report

14. SPONSORING AGENCY CODE

15. SUPPLEMENTARY NOTES
Technical Advisor- Patricia Hilgard , E.P.A.

16. ABSTRACT

This report is a survey and summary of the literature on acrylonitrile. Major aspects of its biological effects, environmental exposure, chemistry, production and use, and regulations are reviewed and assessed. Acrylonitrile is used in a wide variety of plastics, fibers, and elastomers. About 1.5 billion pounds of acrylonitrile are produced annually by the reaction of propylene, air, and ammonia. Low levels of acrylonitrile enter the environment during production, storage, end-product manufacture, and end-use, although extensive monitoring data are not available. Recent evidence shows acrylonitrile to be carcinogenic in animals and possibly carcinogenic in humans. It resulted in birth defects when fed to pregnant rats and caused mutations in some type of bacteria. Short-term exposure to humans causes headache, mucus membrane irritation, dizziness, vomiting and incoordination. Several fatalities have resulted from fumigant use. Direct skin contact produces blisters resembling second-degree burns. In laborator mammals, signs of acrylonitrile intoxication include altered breathing, incoordination, weakness, convulsions, and coma. Signs are especially variable between species and the dose administered. Effects may include central and peripheral nervous system damage; hemorrhaging of the lungs, adrenals, or liver; and depressed sulfhydryl content of the kidneys, liver, or lungs. Long-term administration of acrylonitrile may affect growth, food and water intake, adrenal function, and the central nervous system, depending on the dose.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
Acrylonitrile Carcinogens Chemical Industry Environmental Engineering Regulations Toxicology		Biological & Med. Sciences - biology - clinical medici - toxicology

18. DISTRIBUTION STATEMENT Document is available to the public through the National Technical Information Service, Springfield, Virginia 22151	19. SECURITY CLASS *(This Report)*	21. NO. OF PAGES 251
	20. SECURITY CLASS *(This page)*	22. PRICE PCA12/MF A01

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

EPA 560/2-78-003

INVESTIGATION OF SELECTED POTENTIAL ENVIRONMENTAL CONTAMINANTS: ACRYLONITRILE

By:

Lynne M. Miller
Jon E. Villaume

May 1978
Final Report
EPA Contract No. 68-01-3893
FIRL No. 80G-C4807-01

Prepared For:
Office of Toxic Substances
U.S. Environmental Protection Agency
Washington, D.C. 20460

Document is available to the
public through the
National Technical Information
Service, Springfield, Virginia 22151

1a

Science Information Services Organization
THE FRANKLIN INSTITUTE RESEARCH LABORATORIES
THE BENJAMIN FRANKLIN PARKWAY • PHILADELPHIA, PENNSYLVANIA 19103

NOTICE

This report has been reviewed by the Office of Toxic Substances, U.S. Environmental Protection Agency, and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the Environmental Protection Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

TABLE OF CONTENTS

Page

PREFACE viii

LIST OF TABLES ix

LIST OF FIGURES xi

EXECUTIVE SUMMARY xii

I. PHYSICAL AND CHEMICAL DATA 1
  A. Chemical Structure 1
  B. Properties of the Pure Material 1
  C. Properties of the Commercial Material 3
  D. Chemical Reactions Involved in Use 3
    1. Polymerization 6
    2. Reactions of the Nitrile Group 7
    3. Reactions of the Double Bond 7
    4. Cyanoethylation Reactions 8

II. ENVIRONMENTAL EXPOSURE FACTORS 9
  A. Production 9
    1. Production Processes 9
    2. Quantity Produced 16
    3. Domestic Producers and Production Sites 16
    4. Imports and Foreign Producers 19
    5. Market Price 19
    6. Market Trends 23
  B. Use 25
    1. Major Uses 25
      a. Fibers 27
      b. SAN and ABS Resins 27
      c. Adiponitrile 29
      d. Nitrile Rubber 32
      e. Exports 32
      f. Miscellaneous Uses 35

Page

2. Projected Uses 36
3. Alternatives to Use 37

C. Entry into the Environment 37
1. From Production 37
2. From Waste Handling 41
3. From Storage 42
4. From Transportation 42
5. From End Use 48

D. Disposal and Control Methods 52
1. Waste Disposal 52
2. Control Technology 53

E. Fate and Persistence in the Environment 54
1. Degradation in the Environment 54
a. Biological Degradation 54
b. Chemical Degradation 59
1) Atmospheric Reactions 60
2) Reaction with Water 61
2. Transport Within and Between Media 61
3. Persistence and Bioaccumulation 62

F. Hazards from Combustion 64
1. Thermal Degradation 64
2. Mortality from Pyrolysis Products 65

G. Analytical Detection Methods 67
1. In Air 67
2. In Aqueous Solution 71
3. In By-Products 72
4. In Fumigated Food 72
5. In Biological Material 73

III. BIOLOGICAL EFFECTS 74
A. Humans 74
1. Acute Toxicity 74
a. Inhalation Exposure 74
b. Dermal Exposure 75
c. Fumigant Exposure 76

Page

2. Occupational Exposure 79
    a. Signs and Symptoms 81
    b. Hematological Alterations 84
    c. Effects on Tissues and Organs 85
    d. Possible Carcinogenic Effects 90
3. Controlled Studies 92

B. Nonhuman Mammals 93

1. Absorption and Tissue Distribution 93
2. Biotransformation 94
    a. Biotransformation to Cyanide and Thiocyanate 96
    b. Reaction with Sulfhydryl Groups 100
    c. Coupling with D-Glucuronic Acid 102
    d. Minor Metabolites 102
    e. Route and Dose Dependence of Metabolite Formation 103
3. Toxicity 105
    a. Acute Toxicity 105
        1) Inhalation Exposure 105
            a) Lethal Doses 105
            b) Signs 110
        2) Dermal Exposure 112
            a) Lethal Dose Values 112
            b) Signs 113
            c) Effects on the Skin 114
            d) Effects on the Eye 115
        3) Oral Administration 115
            a) Lethal Dose Values 115
            b) Signs 118
            c) Tissue and Organ Changes 119
        4) Parenteral Administration 120
            a) Lethal Dose Values 120
            b) Signs 120
            c) Effect on the Adrenals 122
            d) Effect on Sulfhydryls 124
            e) Effect on the Circulatory System 129

Page

b. Subacute Toxicity 130
  1) Inhalation Exposure 130
    a) Signs 130
    b) Hematological Effects 133
    c) Pathology 134
  2) Oral Administration 136
    a) No Effect Level 136
    b) Effect on Weight Gain 136
    c) Effect on Clinical Parameters 137
    d) Effect on Organ Weights 138
    e) Pathology 138
    f) Effect on the Adrenals 139
    g) Effect on Glutathione 139
    h) Effect on Reproduction 141
  3) Percutaneous Administration 141
    a) Effect on the Nervous System 141
    b) Effect on Organs 141
c. Chronic Toxicity 142
  1) Inhalation Exposure 142
  2) Oral Administration 143
    a) Effect on Rats 145
    b) Effect on Dogs 152
4. Mechanism of Toxicity 155
  a. Action of Cyanide 155
    1) Cyanide - Metalloprotein Formation 156
    2) Effect on Cytochrome Oxidase 157
    3) Effect on Cyanide Antidotes 158
  b. Direct Action of Acrylonitrile 159
C. Nonmammalian Vertebrates 160
  1. Acute Toxicity 161
    a. Freshwater Fish 161
    b. Marine Fish 163
  2. Subacute Toxicity 164
  3. Effect on Taste of Fish 164

Page

D. Invertebrates 165
  1. Aquatic Organism Toxicity 165
  2. Nonaquatic Organism Toxicity 166
E. Plants 166
F. Microorganisms 168
  1. Microorganisms Used in Mutagenicity Tests 168
  2. Molds on Food 169
  3. Aquatic Microorganisms 169
G. *In Vitro* Studies 170
  1. Effect on Isolated Nerves 170
  2. Effect on Tissue Respiration 170
  3. Effect on Tissue Sulfhydryl Content 171

IV. SPECIAL EFFECTS 172
A. Mutagenicity 172
  1. Broad Bean 172
  2. Fruit Fly 172
  3. Bacterial Systems 173
    a. Ames Standard Plate Method 173
    b. Modified Ames Method 174
    c. Mutagenicity in *Escherichia coli* 176
  4. Yeast 177
  5. Mammalian *In Vitro* Assays 177
  6. DNA Repair Assay 178
B. Cytogenicity 178
C. Teratogenicity 178
D. Carcinogenicity 183

V. REGULATIONS AND STANDARDS 188
A. Federal Regulations 188
  1. Occupational Safety and Health Administration 188
  2. Department of Transportation 189
  3. Environmental Protection Agency 190
    a. Federal Insecticide, Fungicide and Rodenticide Act 190

Page

b. Clean Air Act 191
c. Federal Water Pollution Control Act 191
d. Federal Water Pollution Control Act as Amended by the Clean Water Act of 1977 192
e. Solid Waste Act as Amended by the Resource Conservation and Recovery Act 192
4. Food and Drug Administration 193
B. State Regulations 194
1. Workplace Standards 194
2. Use as a Pesticide 194
3. Water Quality 194
4. Air Emissions 194
5. Food Contact 198
C. Foreign Countries 198
1. United Kingdom 198
2. Canada 198
3. West Germany 199
4. Belgium 199
5. USSR and Bulgaria 199
D. Other Standards 199
E. Current Handling Practices 199
1. Handling, Storage and Transport 199
2. Personnel Exposure 200
3. Accident Procedures 201
VI. EXPOSURE AND EFFECTS POTENTIAL 202
TECHNICAL SUMMARY 208
BIBLIOGRAPHY 213
CONCLUSIONS AND RECOMMENDATIONS 231
APPENDIX A 233

PREFACE

This report is a survey and summary of the literature on acrylonitrile available through April, 1978. Major aspects of its chemistry, environmental exposure, biological effects and regulations are reviewed and assessed. A list of sources employed in locating the information in this review is presented in Appendix A.

This document was prepared by the Franklin Institute Research Laboratory for the Environmental Protection Agency under contract 68-01-3893.

LIST OF TABLES

Table		Page
1.	Nomenclature and Other Identifiers of Acrylonitrile	2
2.	Physical Properties of Acrylonitrile	4
3.	Sales Specifications for Acrylonitrile from 2 Producers	5
4.	U.S. Production and Sales of Acrylonitrile	17
5.	Producers of Acrylonitrile Monomer in the United States	18
6.	Imports of Acrylonitrile into the United States	20
7.	Western European and Far Eastern Producers of Acrylonitrile	21
8.	Market Price of Acrylonitrile in the United States	22
9.	Economics for the Manufacture of Acrylonitrile using the Montedison-UOP Process	24
10.	Producers of Acrylic and Modacrylic Fibers	28
11.	Producers of ABS and SAN Resins	30
12.	Producers of Polybutadiene-AN Elastomers (NBR)	33
13.	Export Data for U.S. Acrylonitrile	34
14.	Emission Factors for Acrylonitrile Manufacture	38
15.	Sources of Atmospheric Contamination of Acrylonitrile During Acrylonitrile Manufacture and Bulk Storage	40
16.	Hazards of Acrylonitrile Transportation	44
17.	Spill Data for Acrylonitrile	46
18.	Acrylonitrile Residues in Walnuts	51
19.	Effect of Acrylonitrile on Anaerobic Activity	59
20.	Concentration of Acrylonitrile at Sampling Sites after Tank Car Spill of 20,000 Gallons on 12/23/73 near Mapelton, Ill.	63
21.	Methods for Determining Acrylonitrile in the Air	69
22.	Processes in which Workers are Exposed to AN at Representative Production Sites	80
23.	Association Between Abnormal Findings and Several Variables Associated with Acrylonitrile Exposure	83
24.	Some Indicators of Peripheral Blood in Donors and Workers Involved in Acrylonitrile Production	84
25.	Blood Values of Workers Engaged in the Production of Acrylonitrile in Russia	86

Table Page

26. Changes in Some Blood Values in Workers Chronically Exposed to Acrylonitrile 89
27. Recovery of Radioactivity from Rats Given Acrylonitrile by A) Oral Doses or B) Inhalation Exposure 95
28. Urinary Metabolites Following the Oral Administration of C-1 (Cyano) Labeled Acrylonitrile 101
29. Metabolites in Rats of ^{14}C-AN Separated by High Pressure Liquid Chromatography 104
30. Inhalation Exposure to Acrylonitrile 106
31. Inhalation Exposure of Acrylonitrile for 4 Hours in Various Mammal Species 107
32. Inhalation Exposure of Rats to Acrylonitrile 109
33. Acute Dermal LD_{50} for Acrylonitrile 112
34. Acute Oral LD_{50} for Acrylonitrile 116
35. Acute Parenteral LD_{50} Values for Acrylonitrile 121
36. Catalase, Sulfhydryl and Lactic Acid Levels in Rats Intoxicated with Acrylonitrile 125
37. Effect of Acrylonitrile (Administered i.p.) on the Hepatic Nonprotein Sulfhydryl Content of Various Species 126
38. Effect of Acrylonitrile on Tissue Sulfhydryl 128
39. Mortality in Animals Exposed to Acrylonitrile over 90 Days 131
40. Hematological Values (Venous Blood) in Rabbits Before and After Exposure to 20 ppm Acrylonitrile 135
41. Effect of Acrylonitrile Administration (21 days) on Hepatic Glutathione in Rats by 2 Routes of Administration 140
42. Changes in Wistar Rats After Exposure to Acrylonitrile (0, 50, 250 mg/m^3) for 3 hr/day, 6 days/week for 6 Months 144
43. Effect of Long-Term Oral Feeding of Acrylonitrile in Rats 146
44. Acrylonitrile in the Drinking Water of Rats 149
45. Gross Pathologic Findings in Male and Female Rats Maintained on Water Containing AN for 12 Months 151
46. Mortality (%) in Several Species After Administration of a Lethal Dose of Acrylonitrile and an Antidote 160
47. Median Tolerance Limit Values (TL_m) for Various Fish Exposed to Acrylonitrile 162
48. Lethal Dose Values of Insects Exposed to Acrylonitrile 167

Table Page

49. Mutagenicity of Acrylonitrile Vapor with *S. typhimurium* Strain TA 1535 175

50. Testing of Acrylonitrile in the Mouse Lymphoma $L_{5178}Y$ Assay 179

51. Incidence of Fetal Alterations Observed During the External or Soft Tissue or Skeletal Examination Among Litters of Rats Receiving Acrylonitrile by Gavage 181

52. Carcinogenicity Bioassays on Rats by Maltoni et al. (1977); Results after 131 Weeks 186

53. Regulations for Acrylonitrile Food Contact and Workplace Standards in Selected States 195

54. Pesticide Restrictions for Acrylonitrile in Selected States 195

55. Water Standards for Acrylonitrile in Selected States 196

56. Air Standards for Acrylonitrile in Selected States 197

57. Respiratory Protection for Acrylonitrile 202

LIST OF FIGURES

Figure Page

1. U.S. Acrylonitrile Capacity by Process 10

2. Production Process for Acrylonitrile 13

3. Acrylonitrile Demand 26

4. Biological Oxidation of Acrylonitrile in Aqueous Systems 56

EXECUTIVE SUMMARY

Acrylonitrile (vinyl cyanide, propenenitrile) is a chemical intermediate used to produce a wide variety of fibers, plastics and elastomers. A small amount is used as a fumigant. About 1.5 billion pounds of acrylonitrile are produced annually by the reaction of propylene, oxygen and ammonia.

Low levels of acrylonitrile enter the environment during production, storage, end-product manufacture, and end-product use, although extensive monitoring data are not available. It is highly reactive chemically and is subject to biological degradation.

Recent evidence shows acrylonitrile to be carcinogenic in animals and possibly carcinogenic in humans. Rats exposed to acrylonitrile for 12 months developed a higher incidence of stomach, central nervous system and ear canal tumors. Acrylonitrile resulted in birth defects when fed to pregnant rats and caused mutations in some types of bacteria. At a textile plant in Camden, S. C., E. I. DuPont de Nemours Company has reported increased cancer among workers exposed to acrylonitrile.

Because of this evidence the Occupational Safety and Health Administration has limited workplace exposure to 2 ppm (time-weighted average) in an Emergency Temporary Standard.

For humans, acrylonitrile is toxic if inhaled, ingested, or applied directly on the skin. Short-term exposure causes headache, mucous membrane irritation, dizziness, vomiting and incoordination. Several fatalities have resulted from fumigant use. Direct skin contact produces blisters resembling second-degree burns. Long-term occupational exposure may affect the central nervous system, liver and blood.

In laboratory mammals, signs of acrylonitrile intoxication include altered breathing, incoordination, weakness, convulsions and coma. Signs vary widely in different species and at different doses. Effects may include central and peripheral nervous system damage; hemorrhaging of the lungs, adrenals, or livers; and depressed sulfhydryl content of the kidneys, liver or lungs.

Long-term administration of acrylonitrile may affect growth, food and water intake, adrenal function, and the central nervous system, depending on the dose.

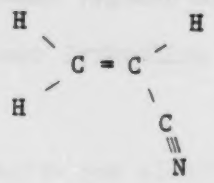
In mammals, acrylonitrile is broken down to cyanide (which is further metabolized to thiocyanate), and also reacts with sulfhydryl groups. The toxic action may be due to cyanide formation, but is more likely due to the direct effects of acrylonitrile.

Acrylonitrile is toxic to several species of fish, insects and microorganisms.

I. PHYSICAL AND CHEMICAL DATA

A. Chemical Structure

Acrylonitrile (AN) is a flammable colorless liquid of the following planar structure:



All bond angles equal about 120°. Bond distances have been estimated as follows: $C-H \sim 1.09$ Å; $C-C \sim 1.46$ Å; $C=C \sim 1.38$ Å; $C \equiv N \sim 1.16$ Å (Wilcox and Goldstein, 1954). Table 1 presents synonyms and other identifiers.

B. Properties of the Pure Material

Some of the important physical properties of acrylonitrile are listed in Table 2. Acrylonitrile is miscible with most organic solvents including acetone, benzene, carbon tetrachloride, ether, ethyl acetate, ethyl alcohol, ethylene cyanohydrin, liquid carbon dioxide, methyl alcohol, petroleum ether, toluene and xylene (American Cyanamid, 1959). The solubility of acrylonitrile in water is listed in Table 2. Pure acrylonitrile is subject to self-polymerization with rapid pressure development.

Acrylonitrile has a flash point of 0°C so ignition occurs readily and the vapors are explosive. It forms explosive mixtures with air at about 3.05 to 17% by volume (explosive range; Patty, 1963).

Table 1

Nomenclature and Other Identifiers of Acrylonitrile

Item	Data
Chemical Abstracts Service (CAS) 9th Collective Index name:	2-Propenenitrile
CAS Registry No.:	107-13-11
EPA Toxic Substances List No.:	R037-2101
NIOSH Registry No.:	AT 52500
EPA Toxic Substances List No.:	R037-2101
Synonyms[a]:	ACRN
	AN
	Cyanoethylene
	2-Propenenitrile
	Vinyl cyanide
	VCN
Standard Industrial Code	2822; 2824
Wiswesser Line Notation:	NC1U1
Molecular Formula:	C_3H_3N
Chemical Formula:	$CH_2 = CHCN$

[a] fumigant formulations with acrylonitrile included the names Acrylon, Carbacryl, ENT 54, Fumigrain and Ventox; these are no longer manufactured.

The threshold odor level for acrylonitrile determined by 16 panelists (total of 104 observations) averages 18.6 ppm ranging from 0.0031 to 50.4 ppm (Baker, 1963).

C. Properties of the Commercial Material

Technical-grade acrylonitrile is a highly pure product (greater than 99% pure, excluding any added stabilizers). The specifications for acrylonitrile available from DuPont and Monsanto appear in Table 3.

Except for water, impurities are present only in ppm. Possible contaminants include acetone, acetonitrile, acetaldehyde, iron, peroxides and hydrocyanic acid (Table 3). Water, present at a maximum of about 0.5%, improves the stability of the product. Highly pure acrylonitrile may polymerize spontaneously. Yellowing upon long exposure to light indicates photoalteration to saturated derivatives. Commercial acrylonitrile is stabilized against self-polymerization and color formation with water and methylhydroquinone. However, hazardous polymerization may still occur in the absence of oxygen, upon exposure to visible light or in the presence of alkali (Department of Transportation, 1974).

D. Chemical Reactions Involved in Use

Acrylonitrile is a versatile chemical intermediate. Its reactions may involve the cyano group (CN), the double bond (C = C) or both. Only a few representative commercial reactions are listed below, the most important being polymerization. End uses of acrylonitrile and the preparation of these products are presented in Section II-B. A thorough discussion of

Table 2

Physical Properties of Acrylonitrile
(American Cyanamid, 1959, 1974)

Item	Data
Appearance	colorless liquid
Boiling Point	77.3°C at 760 mm pressure
Density	0.8060 (20°C)
	0.8004 (25°C)
Flash Point (Tag Open Cup)	0°C
(Closed Cup)	-4.4°C
Freezing Point	-83.55 ± 0.05°C
Ignition Temperature	481°C
Molecular Weight	53.06
Octanol/H_2O Partition Coefficient	0.12[a]
Odor	faintly pungent
Refractive Index	$n_D^{25} = 1.3888$
% Solubility in Water[b]	7.2% (0°C)
	7.35% (20°C)
	7.9% (40°C)
Vapor Pressure (mm Hg)	50 (8.7°C)
	100 (23.6°C)
	250 (45.5°C)
	500 (64.7°C)
	760 (77.3°C)
Partial Vapor Pressure, Water azeotrope	$\text{Log } P = 7.518 - \frac{1644.7}{T°K}$ (i.e., 80 mm at 20°)
Conversion Factor for Vapor (25°C; 760 mm Hg)	1 mg/l = 460.5 ppm 1 mg/l X 10^3 = mg/m^3 1 ppm = .002170 mg/l 1 mg/l = 1 ppm, in water

---

[a] Dorigan et al., 1976; antilog of -0.92

[b] AN is miscible with most organic solvents

Table 3

Sales Specifications for Acrylonitrile from 2 Producers (DuPont, 1977a; Monsanto, 1977a)

SPECIFICATIONS	DuPont	Monsanto
Acetone, ppm max.	n.r.	300
Acetonitrile, ppm max.	500	500
Aldehydes, as Acetaldehyde, ppm max.	50	50
Iron, ppm max.	0.1	0.2
HCN, ppm max.	10	5
Refractive Index at 25°C	1.3880-1.3892	1.3880-1.3892
Peroxides, ppm max. as H_2O_2	0.3	1.0
Water, %	0.25-0.45	0.25-0.45
Nonvolatile Matter, ppm max.	100	100
Appearance	Clear and free	Clear and free
Inhibitor, MEHQ* ppm	35-50	35-50
Acidity, as Acetic Acid, ppm max.	35	20
pH, 5% Aqueous Solution	5.5-7.5	n.r.

n.r. = not reported

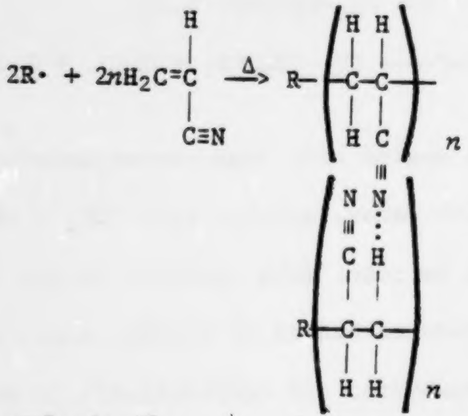
* MEHQ = methylhydroquinone

the industrial chemistry of acrylonitrile is found in American Cyanamid (1959).

1. Polymerization

Polymerization, forming high molecular-weight products, is the most important commercial reaction of acrylonitrile. Acrylonitrile does not polymerize in the absence of initiators but does polymerize when irradiated with light (wavelength < 2900 Å) or when present with active radicals. Oxygen is a powerful inhibitor of the polymerization of acrylonitrile (Bamford and Eastmond, 1964)

Acrylonitrile can be polymerized using bulk, solution, suspension or emulsion techniques to produce polyacrylonitrile:



Acrylonitrile Polyacrylonitrile

As shown above, cyano groups participate in hydrogen bonding with adjacent hydrogen atoms. Polyacrylonitrile can be copolymerized with a small amount of methyl methacrylate or vinyl pyridine to introduce reactive dyeing sites; pure polyacrylonitrile cannot be dyed using conventional techniques (Seymour, 1975).

It can be copolymerized with other monomers. Examples of acrylonitrile copolymers include nitrile rubber, acrylonitrile-butadiene-styrene (ABS) and styrene-acrylonitrile (SAN) resins. Terpolymers of acrylonitrile or methacrylonitrile are the so-called barrier resins (Seymour, 1977). These products are discussed in Section II-B-1-f. The production and properties of acrylonitrile polymers are reviewed in Bamford and Eastmond (1964).

2. Reactions of the Nitrile Group (American Cyanamid, 1969; Fugate, 1963)

Acrylonitrile hydrated at 100°C with 84.5% sulfuric acid produces acrylamide sulfate, which yields acrylamide upon neutralization as shown below:

$$CH_2{=}CHCN + H_2O + H_2SO_4 \longrightarrow CH_2{=}CHCONH_2 \cdot H_2SO_4$$

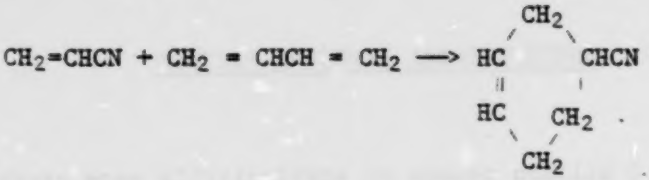
$$CH_2{=}CHCONH_2 \cdot H_2SO_4 + CaO \longrightarrow CH_2{=}CHCONH_2 + CaSO_4 + H_2O$$

When acrylonitrile is heated with less concentrated sulfuric acid or if acrylamide is heated with water, acrylic acid ($CH_2 = CHCOOH$) is formed.

Acrylonitrile allowed to react with alcohols in the presence of concentrated sulfuric acid produces esters of acrylic acid, with acrylamide sulfate formed as an intermediate. If acrylonitrile is mixed with olefins or alcohols in concentrated sulfuric acid, N-substituted acrylamides are formed.

3. Reactions of the Double Bond (American Cyanamid, 1959)

Acrylonitrile has an activated double bond which acts as a dienophile in the Diels-Alder Reaction. When treated with aliphatic or alicyclic compounds containing conjugated carbon-to-carbon double bonds cyclic products are produced. An example is the reaction with butadiene:

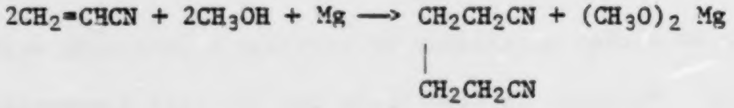


Δ-3-tetrahydrobenzonitrile

Acrylonitrile in the presence of catalysts can be hydrogenated to propionitrile which can be further hydrogenated to n-propylamine:

$$CH_2 = CHCN \xrightarrow{H_2} CH_3CH_2CN \xrightarrow{2H_2} CH_3CH_2CH_2NH_2$$

Reductive coupling of acrylonitrile (shown below with magnesium and methanol) produces adiponitrile:



$$2CH_2{=}CHCN + 2CH_3OH + Mg \longrightarrow \begin{array}{l} CH_2CH_2CN \\ | \\ CH_2CH_2CN \end{array} + (CH_3O)_2\,Mg$$

4. Cyanoethylation Reactions

Cyanoethylation reactions involve the reaction of acrylonitrile with active hydrogen compounds (AH molecules). Examples of AH molecules are: water, alcohols, ammonia, amines, mercaptans, aldehydes, inorganic acids and their salts, aldehydes and ketones. The generalized reaction can be written:

$$CH_2{=}CHCN + AH \longrightarrow ACH_2CH_2CN$$

(American Cyanamid, 1959).

The cyanoethylation of 3 nucleosides (pseudouridine, inosine, 4-thiouridine) by acrylonitrile has been studied as a model for the cyanoethylation of intact tRNA (Ofengand, 1967).

II. ENVIRONMENTAL EXPOSURE FACTORS

More than 1.5 billion pounds of acrylonitrile were produced by four domestic manufacturers during 1976 (U.S. International Trade Commission, 1976). Aspects of acrylonitrile production, use, and entry into the environment will be discussed in the following sections.

A. Production

1. Production Processes

In 1893 the French chemist Moreau first prepared acrylonitrile by the dehydration of either acrylamide or ethylene cyanohydrin with phosphorus pentoxide. However, acrylonitrile was not used commercially until the late 1920's when German chemists used it to make oil-resistant rubber. Manufacture of acrylonitrile began in 1940 in the United States (Fugate, 1963).

Several processes for the production of acrylonitrile monomer have been commercialized (Figure 1). Before 1960 the dominant manufacturing process was the catalytic reaction of acetylene and hydrogen cyanide in the presence of a cuprous chloride catalyst, according to the equation:

$$\underset{\text{acetylene}}{C_2H_2} + \underset{\substack{\text{hydrogen}\\\text{cyanide}}}{HCN} \xrightarrow{CuCl} \underset{\text{AN}}{CH_2 = CHCN}$$

Until the mid 1960's other less widely used processes included:

(i) the catalytic dehydration of ethylene cyanohydrin

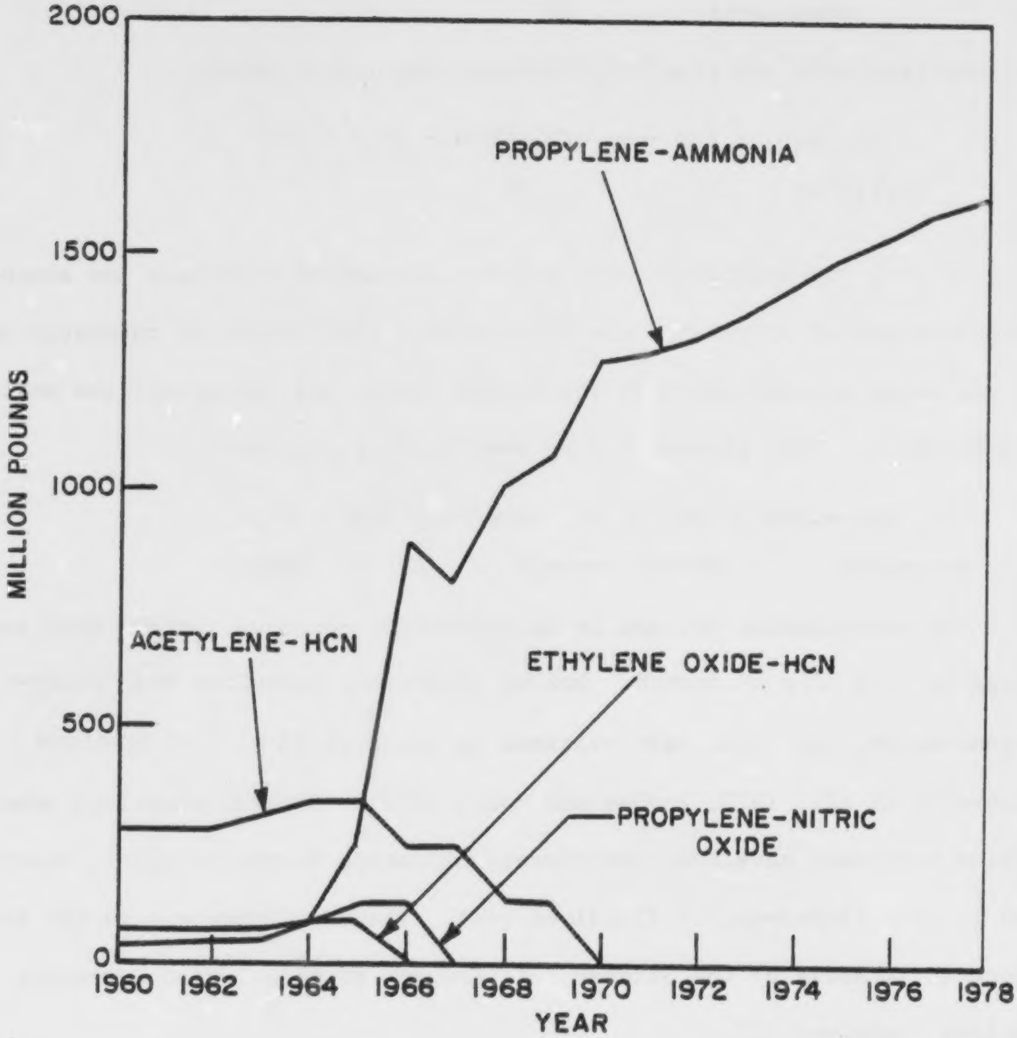


Figure 1. U.S. Acrylonitrile Capacity by Process
(based on Idol, 1974)

$$(CH_2)_2O + HCN \longrightarrow CH_2(OH)CH_2CN$$

ethylene oxide   hydrogen cyanide   ethylene cyanohydrin

$$CH_2(OH)CH_2CN \longrightarrow CH_2 = CHCN + H_2O$$

cyanohydrin   AN

ii) the catalytic reaction of propylene with nitric oxide

$$4CH_2{=}CHCH_3 + 6NO \longrightarrow 4CH_2{=}CHCN + 6H_2O + N_2$$

propylene   nitric oxide   AN

In 1960 the catalytic vapor phase oxidation of propylene and ammonia (ammoxidation of propylene) was introduced. This method is currently used by all major manufacturers in the United States and throughout the world (Idol, 1974). This process can be described as follows:

$$2CH_2{=}CHCH_3 + 2NH_3 + 3O_2 \longrightarrow 2CH_2{=}CHCN + 6H_2O$$

propylene   ammonia   oxygen   AN   water

The ammoxidation process is an exothermic reaction, with a heat release of 17.6 kJ/g AN formed.* Adding by-product reactions and catalyst regeneration, the total heat released is about 21.93 kJ/g AN produced (Schwartz et al., 1975; Hughes and Horn, 1977). Several propylene ammoxidation processes have been introduced, differing in the catalyst, recovery and reactor (fixed-bed or fluidized bed). The most important is the Sohio process, patented by the Standard Oil Company of Ohio, which currently employs "Catalyst 41".

This catalyst, introduced by Sohio in 1972, is a uranium-free fluid-bed catalyst based on bismuth phosphomolybdate. Acrylonitrile yields are theoretically increased 35% over those with the older uranium based cata-

* 1 kJ= 4.18 kcal

lyst (catalyst 21) used from 1967 to 1973 (Townsend, 1974). The original Sohio catalyst (Catalyst A) was used from 1960 to 1967 and was of bismuth phosphomolybdate composition.

In 1976, Sohio of the United States was licensed by the Nitto Chemical Industry Co. (Japan) to use Nitto's catalyst ("NS773A") for the production of acrylonitrile (Anon., 1976a; Anon., 1977a). This catalyst is currently used by Nitto in Japan.

In the Sohio process the feedstock consists of anhydrous fertilizer grade ammonia, propylene and air which yield more than 0.85 pounds of acrylonitrile per pound of propylene feed (Anon., 1975). The theoretical yield is 1.26 pounds of acrylonitrile per pound of propylene feed (Townsend, 1974). About 0.1 pound each of acetonitrile and hydrogen cyanide are produced as by-products per pound of acrylonitrile produced.

As of 1976 only Vistron and duPont marketed the byproduct acetonitrile. About 75% of the by-product hydrogen cyanide is marketed (Vistron, 1978, pers comm.). Remaining acetonitrile and hydrogen cyanide are either incinerated or disposed of by deep well injection (Schwartz et al., 1975). See Section II-C-2 for more information on waste disposal.

In the flow scheme shown in Figure 2, the feeds are mixed and introduced into a fluid bed catalytic reactor which operates at 5 to 30 psig

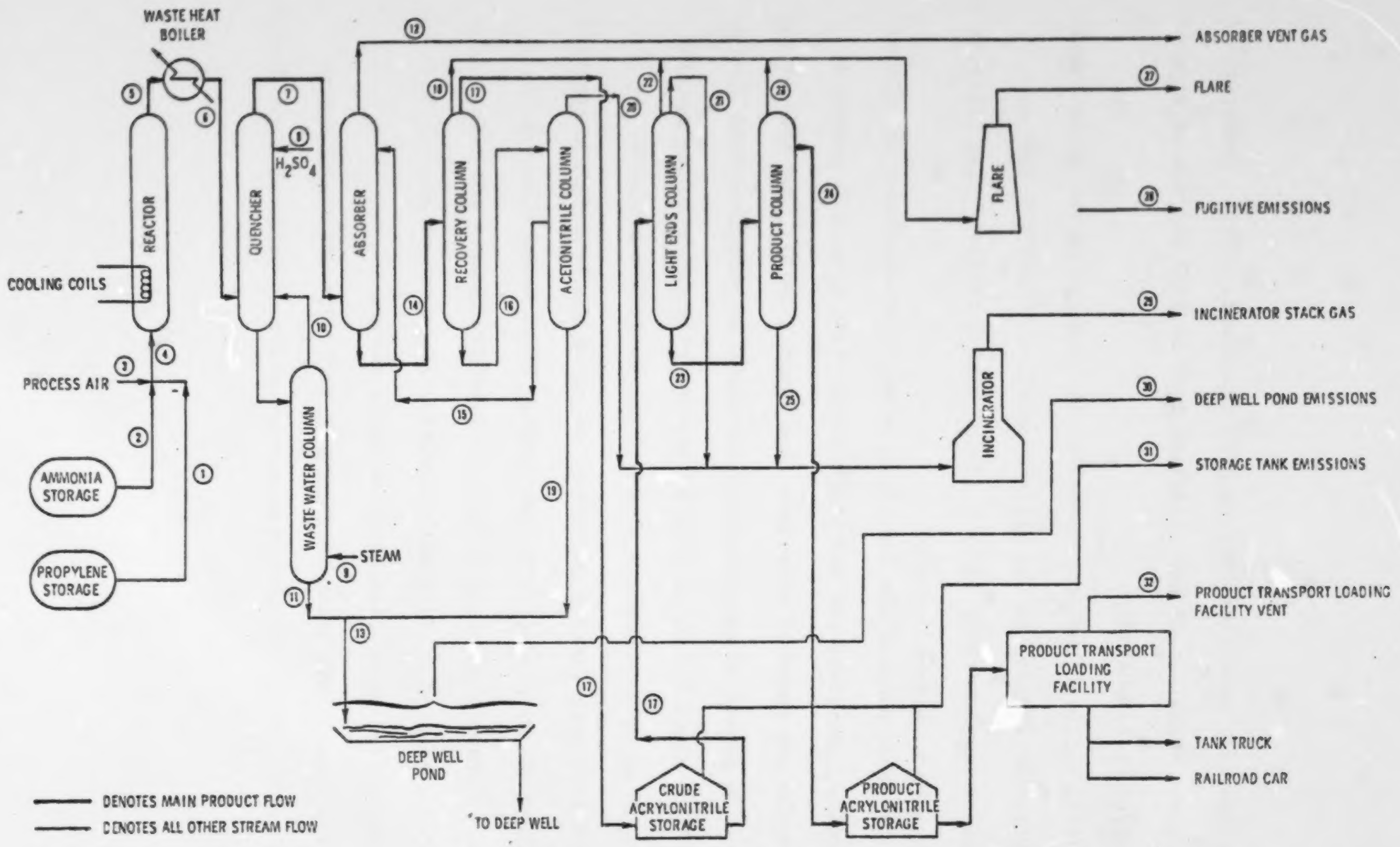

WASTE HEAT BOILER
COOLING COILS
REACTOR
PROCESS AIR
AMMONIA STORAGE
PROPYLENE STORAGE
QUENCHER
H_2SO_4
WASTE WATER COLUMN
STEAM
ABSORBER
RECOVERY COLUMN
ACETONITRILE COLUMN
LIGHT ENDS COLUMN
PRODUCT COLUMN
FLARE
INCINERATOR
DEEP WELL POND
TO DEEP WELL
CRUDE ACRYLONITRILE STORAGE
PRODUCT ACRYLONITRILE STORAGE
PRODUCT TRANSPORT LOADING FACILITY
ABSORBER VENT GAS
FLARE
FUGITIVE EMISSIONS
INCINERATOR STACK GAS
DEEP WELL POND EMISSIONS
STORAGE TANK EMISSIONS
PRODUCT TRANSPORT LOADING FACILITY VENT
TANK TRUCK
RAILROAD CAR
DENOTES MAIN PRODUCT FLOW
DENOTES ALL OTHER STREAM FLOW
①
②
③
④
⑤
⑥
⑦
⑧
⑨
⑩
⑪
⑫
⑬
⑭
⑮
⑯
⑰
⑱
⑲
⑳
㉑
㉒
㉓
㉔
㉕
㉗
㉘
㉙
㉚
㉛
㉜

Figure 2. Production Process for Acrylonitrile (Hughes and Horn, 1977 which was redrawn from Schwetz et al., 1975)

Figure 2 (continued)

Stream number	Description
1	Propylene feed
2	Ammonia feed
3	Process air
4	Reactor feed
5	Reactor product
6	Cooled reactor product
7	Quenched reactor product
8	Sulfuric acid
9	Stripping steam
10	Wastewater column volatiles
11	Wastewater column bottoms
12	Absorber vent gas
13	Acrylonitrile plant wastewater
14	Absorber bottoms
15	Water recycle
16	Crude acetonitrite
17	Crude acrylonitrile
18	Recovery column purge vent
19	Acetonitrite column bottoms
20	Acetonitrile
21	Hydrogen cyanide
22	Light ends column purge vent
23	Light ends column bottoms
24	Product acrylonitrile
25	Heavy ends
26	Product column purge vent
27	Flare
28	Fugitive emissions
29	Incinerator stack gas
30	Deep well pond emissions
31	Storage tank emissions
32	Product transport loading facility vent

and 750° to 950°F (Anon., 1975). The following discussion is entirely from Hughes and Horn (1977) to whom the reader is referred for more detail. Cooled reactor effluent (Stream 6) is sent to a quencher. Here, additional product cooling takes place and excess ammonia is removed. Bottoms from the quencher are sent to the wastewater column (Stream 9). The quenched reactor products (Stream 7) are sent to the absorber for recovery of acrylonitrile, hydrogen cyanide and acetonitrile. Absorber vent gas may be routed to the atmosphere (Stream 12).

Bottoms from the absorber are sent to the recovery column where crude acrylonitrile is separated from crude acetonitrile. Crude acetonitrile is sent to the acetonitrile column. Acetonitrile column bottoms are sent to a deep well pond (Stream 19) while acetonitrile is purified or is incinerated (Stream 20). Crude acrylonitrile is purified after storage (Stream 17) first in the light-ends column and then in the product column. Hydrogen cyanide from the light ends column (Stream 21) and product column bottoms, and heavy ends from the product (Stream 25) may be incinerated or purified. In Figure 2 are shown additional process streams which are disposed of by flare (combustion device), incineration and/or deep well injection. These and other streams will be discussed further in Section II-C as possible sources of acrylonitrile to the environment.

Montedison-UOP has recently introduced a modified process for the ammoxidation of propylene using a different catalyst than Sohio (Pujado, et al., 1977). This process, as does Sohio's, uses a fluidized bed reactor and a feed stock consisting of propylene and ammonia. The Montedison process claims a more energy-efficient product separation and recovery system. It does not appear, however, that any process will be able to economically compete with Sohio's in the foreseeable future in the U.S. (Lowenbach et al., 1978).

2. Quantity Produced

During 1976 more than 1517 million pounds of acrylonitrile monomer were produced in the United States (U.S. International Trade Commission, 1976). This represents a 53% increase in production since 1966. Within this decade, however, year to year production has been erratic (Table 4).

3. Domestic Producers and Production Sites

There are four manufacturers of acrylonitrile monomer in the United States: American Cyanamid Co., E. I. DuPont de Nemours and Co. Inc., Monsanto Co. and Vistron Corp. Their total production capacity is 1650-1710 million pounds. Individual plant capacities and sites are listed in Table 5. During 1976 DuPont had the largest production capacity, 610 million pounds (SRI, 1977). However, in 1977 Monsanto's capacity was increased, so that Monsanto became the largest domestic producer (Anon., 1977b).

Although plant capacities are known, it is difficult to obtain information on actual plant production. During 1976 Monsanto apparently operated at capacity for most of the year (Monsanto Company, 1976). SOHIO (Vistron) produced 341 million pounds of acrylonitrile during 1976 (Standard Oil Co., 1976), which is about 15% below capacity. American Cyanamid was expected to produce 245 million pounds of acrylonitrile during 1977 (American Cyanamid, 1977).

Historically, acrylonitrile was produced by Union Carbide (Institute, W.Va.) from 1954 to 1966 and by B. F. Goodrich (Calvert City, Ky.) from 1954 to 1972. The Union Carbide facility is now involved in the production of an intermediate polymer which uses acrylonitrile as a starting material. The Goodrich facility is no longer involved with acrylonitrile manufacture (Union Carbide, 1977; B. F. Goodrich, 1977).

Table 4

U.S. Production and Sales of Acrylonitrile[a]

	Production (1,000 pounds)	Sales (1,000 pounds)	Value of Sales (1,000 $)	Average Cost per pound ($)
1976	1,517,830	600,987	147,144	0.24
1975	1,214,550	523,694	122,459	0.23
1974	1,411,749	511,701	95,171	0.19
1973	1,354,160	480,715	50,878	0.11
1972	1,114,749	459,985	49,259	0.11
1971	978,897	429,153	44,364	0.10
1970	1,039,257	547,124	59,812	0.11
1969	1,156,585	561,632	65,950	0.12
1968	1,020,957	N.R.	N.R.	N.R.
1967	670,764	270,454	31,875	0.12
1966	716,074	318,169	40,285	0.13

N.R. = not reported

[a] source: U.S. International Trade Commission 1973-1976
U.S. Tariff Commission 1966-1972

Table 5

Producers of Acrylonitrile Monomer in the United States (Vistron, 1978; SRI, 1977; Anon., 1977b.; Monsanto, 1976)

	Capacity (Millions of Lbs.)
American Cyanamid Co. Industrial Chemicals and Plastics Div. New Orleans, LA	200-240
E.I. DuPont de Nemours & Co., Inc. Polymer Intermediates Dept. Beaumont, TX	350
E.I. DuPont de Nemours & Co., Inc. Industrial Chemicals Dept. Memphis, TN	260
Monsanto Co. Monsanto Polymers and Petrochemicals Co. Alvin, TX	440-460
Texas City, TX	420[a]
Vistron Corporation	290
Standard Oil Co. (Ohio) Lima, OH	110

---

[a] Annual Report Monsanto Co., 1976.

4. Imports and Foreign Producers

Imports of acrylonitrile into the U.S. during 1976 amounted to more than 13 million pounds and came almost exclusively from The Republic of China (51.7%) and Japan (48.2%) (Table 6; U.S. Bureau of the Census 1976a). During 1975 acrylonitrile was imported mainly from Japan (32.3%) and the United Kingdom (67.5%); since 1970 West Germany and the Netherlands have also exported acrylonitrile to the U.S.

The current W. European and Far Eastern acrylonitrile producers are listed in Table 7. The specific foreign producers exporting acrylonitrile into the United States are not known, only the total amount per country. As shown in Table 6, total imports steadily increased from 1970 to 1974 but dropped in 1975; 1976 levels were below the peak 1974 levels. Historically, high import levels were attained during 1965, 1968 and 1969 (1204, 35 and 55 thousand pounds, respectively; U.S. Bureau of the Census (1965-1976a).

5. Market Price

The current market price of acrylonitrile is listed in Table 8. The major producers sell acrylonitrile mainly bulk (i.e., full truck or car loads); the price ranges from 27 to 27½¢/lb f.o.b. Small quantities may be purchased from distributors, the price depending on the quantity ordered.

The price of acrylonitrile was higher during the 1940's and early 1950's. The list price of acrylonitrile declined from 53¢ per pound in 1952 to about 14½¢/lb in 1961. Prices remained at about 14½¢/lb during 1961 to 1974, except for a 2½¢ increase in 1964 and 1965. In 1974, acrylonitrile cost 14½¢ to 19½¢ (Idol, 1974; Anon., 1974).

Table 6

Imports of Acrylonitrile into the United States[a]

	Total (lbs)	% of Total, by Country
1976	13,362,306	
China		51.7
Japan		48.2
Other		0.1
1975	7,152,019	
Japan		32.3
U.K.		67.5
Other		0.2
1974	15,386,990	
U.K.		73.9
Nethlds.		17.8
W. Germ.		5.4
Japan		2.9
1973	18,405	
U.K.		97.6
Other		2.4
1972	2,492	
U.K.		60.2
Nethlds.		39.8
1971	6,614	
Nethlds.		100
1970	265	
Germany		100

---

[a] source: U.S. Bureau of the Census, U.S. Imports for Consumption and General Imports 1970-1976.

Table 7

Western European and Far Eastern Producers of Acrylonitrile (Olson, 1977)

Country	Producer	1977 Capacity (million lbs.)
Austria	Erdol-Chemie	94
France	Norsolor	220
	PUK	110
Germany	Erdol Chemie	573
	Hoechst	198
Italy	ANIC	176
	Montedison	159
	Rumianca	176
Japan	Asahi	517
	Mitsubishi	176
	Mitsui Toatsu	132
	Nitto Chemical	310
	Showa Denko	153
	Sumitomo	280
Korea	Tong Suh Petrochemical	110
Netherlands	DSM	298
Republic of China	China Petrochemical	154
Spain	Paular	198
U.K.	Border	176
	Monsanto	265

Table 8

Market Prices of Acrylonitrile in the United States
(12/1/77; industrial sources)

Producer:	**Quotation**
American Cyanamid	27 ¢/lb.; f.o.b.; bulk
DuPont	27 1/2c/lb.; f.o.b.; bulk
Monsanto	27 c/lb.; f.o.b.; bulk
Vistron	27 ¢/lb.; f.o.b.; bulk
Distributor:[a]	
Aldrich Chemical Co., Inc. 159 Forrest St., Metuchen, NJ 940 W. St. Paul Ave., Milwaukee, WI	$2.00/100 g; $4.45/kilo; $8.90/3 kilo
East Falls Corp.[a] Lee Blvd., Frazer, PA	53 ¢/lb. for 1-10 drums (55 gal/drum) 52 ¢/lb for 4-9 drums 49 ¢/lb for 10-19 drums 47 ¢/lb for 20 drums - truckload (shipped collect)
Webb Chemical Corp.[b] Jarman St. Muskegon Hts., MI	40 ¢/lb. for 1-10 drums (55 gal/drum) 37 ¢/lb. for 11-59 drums 35 ¢/lb. for >60 55 drums (shipped collect)

---

[a] not a comprehensive list of distributors; most manufacturers will not divulge this information.

[b] purchased from DuPont.

Stobaugh and Townsend pointed out four factors underlying the decline in the price of acrylonitrile (and other petrochemicals) (Townsend, 1974): a) increasing scale economies of larger production facilities; b) efficiency of accumulating production experience (e.g., new catalysts improving yield); c) more producers [1 producer of AN in 1951 to a high of 6 in 1960-1965]; d) more standardized product. The most important factor, however, is the significant reduction in the production cost since the introduction of the Sohio process for acrylonitrile manufacture.

The price of acrylonitrile has risen since 1974, partly due to inflation, the increased price of raw materials and higher capital costs. Raw materials now represent about 75% of the production cost. Capital costs are three times what they were in the 1960's for the same sized plants, particularly due to environmental control equipment (Olson, 1977). Latest price increases of 1c per lb since January, 1977 reflect increased acrylonitrile demand. Prices are forecasted to continue to reflect the rising cost of propylene and ammonia (Anon., 1977c).

Table 9 shows a breakdown of factors contributing to the 1977 transfer price of acrylonitrile produced by ammoxidation using a Montedison-UOP catalyst; up-to-date information for SOHIO's catalyst 41 was not available.

6. Market Trends

The average annual growth of acrylonitrile has been about 11% during 1965 to 1975 (Anon., 1977b). In 1975 the market fell due to decreased fiber demand but has now recovered (Pujado et al., 1977). An annual growth rate of 8 to 10% is estimated for 1977 to 1981, especially attributable to plastics demand (Anon., 1977b). Further growth is expected during the early 1980's from increased demands for polyacrylamide, to be used in tertiary oil recovery (Pujado et al., 1977). Growth of individual markets for acrylonitril

Table 9

Economics for the Manufacture of Acrylonitrile Using the Montedison-UOP Process[a] (Pujado et al., 1977)

Capital Cost	\$ MM[b]
Battery limits capital cost (BLCC)	35.3
Offsites (@ 20% of BLCC)	7.1
Estimated erected cost (EEC)	42.4
Estimated working capital (EWC)	8.2
Estimated total investment	50.6
Operating expenses	**Cost Acrylonitrile ¢/lb.**
Raw materials Propylene, 92% purity @ 9¢/lb. Ammonia, fertilizer grade @ 6.5¢/lb.	14.7
Catalyst and chemicals	1.4
Utilities	0.4
Labor Labor, supervision and fringe benefits	0.3
Maintenance, @ 3% of EEC	0.6
Expenses Property taxes, insurance, interest on capital (@ 8%), interest on EWC (@ 9%), depreciation, general plant overhead	3.3
Credits HCN @ 22¢/lb	(1.2)
Return on investment @ 30% of EEC	5.8
Acrylonitrile transfer price	25.3

[a] based on 100,000 metric tons/year; propylene ammoxidation process
[b] millions of dollars

are discussed in Section II-B-1.

The future of acrylonitrile is tied to the availability of propylene and ammonia. Acrylonitrile currently uses about 15% of the total supply of propylene (Ponder, 1976). Although propylene was in tight supply during 1976 (Anon., 1976b) a sufficient quantity is expected in the future (Anon., 1977e; Anon., 1977b). No shortages of ammonia are indicated, although large amounts of ammonia will probably be imported to the U.S. by 1980 (Olson, 1977).

B. Use

1. Major Uses

The major uses of acrylonitrile include acrylic and modacrylic fibers (50%), acrylonitrile-butadiene-styrene (ABS) and styrene-acrylonitrile (SAN) resins (20%), adiponitrile (10%), nitrile rubber (5%), exports (10%), as well as miscellaneous applications (5%) including use as a pesticide (Anon., 1977b). Acrylonitrile demand (lb/year) for each of these uses appears in Figure 3 and totaled almost 1.5 billion pounds during 1976 (Anon., 1977c).

The manufacturers of acrylonitrile use much of their production captively as suggested by the difference between 1976 domestic production (>1.5 billion lbs.) and sales 0.6 billion pounds; Table 4). Among the major users of acrylonitrile are its manufacturers. During 1977 American Cyanamid will use about 75% of its production captively (American Cyanamid, 1977). On the other hand, Vistron will use less than 10% of its production captively (Vistron, 1978). Worldwide, captive consumption of acrylonitrile was about 58% of production during 1976 (Olson, 1977). Information on the consumption of acrylonitrile in each of the major use-categories follows.

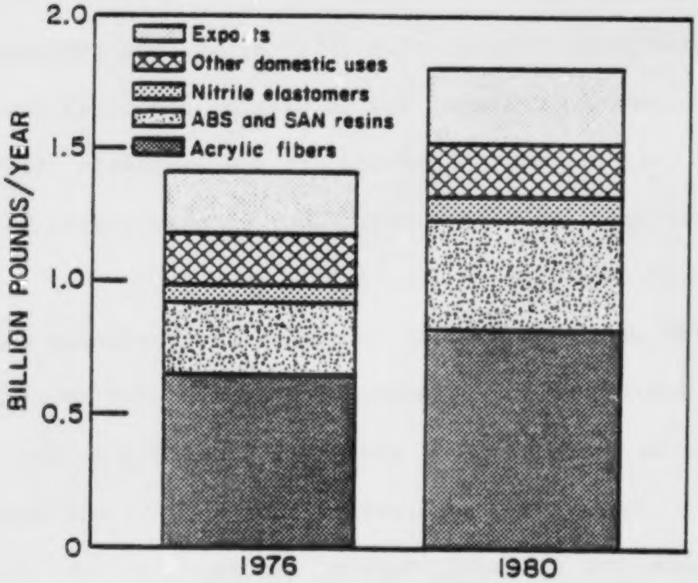


Figure 3. Acrylonitrile Demand
(based on Anon., 1977c)

a. Fibers

By definition, acrylic fibers contain at least 85% AN while modacrylic fibers contain 35 to 85% acrylonitrile. Acrylonitrile is polymerized with standard redox catalysts. The polymer is separated as a powder (m.w. 75-150 x 10^3) then dry spun or wet spun. Co-monomers for acrylic fibers include vinyl acetate, acrylic esters and acrylamide. Modacrylic co-monomers may include vinyl chloride or vinylidene dichloride (Holker, 1975).

Acrylic and modacrylic fibers are used, for example, in apparel (65%; e.g. knits, broadwoven fabrics, pile fabrics) in home furnishings (32%; e.g. carpets, blankets, drapery) and industrial and other uses (30%; e.g. sandbags, hair pieces). Acrylics are the synthetic fibers that most closely resemble wool and compete with wool in the carpet, knitwear and woven good market (Stobaugh et al., 1971).

During 1976 about 552 million pounds of acrylonitrile and polyacrylonitrile copolymers were produced for acrylic and modacrylic fiber use. This represents an increase of 4% over 1975 levels (U.S. Int. Trade Comm., 1975 and 1976). There are 5 manufacturers of acrylic and modacrylic fibers: American Cyanamid, Dow Badische, Dupont, Eastman Kodak and Monsanto. Production sites, capacities, and trade names are listed in Table 10.

b. SAN and ABS Resins

Acrylonitrile satisfies only 25-30% of the raw materials needed to produce styrene-acrylonitrile (SAN) and acrylonitrile-butadiene-styrene (ABS) resins (Stobaugh et al., 1971). However, these resins demand 20% of acrylonitrile production.

SAN resins (which contain 20-35% AN) are produced by allowing acrylonitrile to react with styrene in one of several polymerization processes: emulsion, solution, continuous mass or suspension. ABS resins are produced

Table 10

Producers of Acrylic and Modacrylic Fibers
(SRI, 1975)

	Capacity (millions of lbs.)	Tradenames
American Cyanamid Co. Fibers Division Pensacola, Fla.	120	Creslan (acrylic)
Dow Badische Co. Williamsburg, Va.	70	Zefran II (acrylic)
E. I. DuPont de Nemours & Co. Inc. Textile Fibers Dept.		
Camden, S.C.	170	Orlon (acrylic)
Waynesboro, Va.	140	(acrylic)
Eastman Kodak Co. Tennessee Eastman Co., div. Kingsport, Tenn.	45	Verel (modacrylic)
Monsanto Co. Monsanto Textiles Co. Decatur, Ala.	240	Acrilan (acrylic and modacrylic)
Union Carbide Corp. Films-Packaging Div. Charleston, W. Va.	30	Dynel (modacrylic)

by the emulsion grafting of styrene and acrylonitrile (70:30) onto rubber latex or by mass suspension grafting of styrene and acrylonitrile on dissolved polybutadiene followed by cross-linking of the rubber particle (Monsanto, 1977b; Bamford & Eastmond, 1964).

SAN resins are used in compounding (32%), housewares (18%), molded packaging (10%), export (12%), automotive (6%), small appliances (4%) and miscellaneous uses (18%) (Anon., 1978a).

Major markets for ABS resins include pipe (29%), automotive (18%), large appliances (14%), small appliances (5%), recreational vehicles (8%), business machines and telephones (5.2%), furniture, luggage and packaging (6.1%), exports (3.2%) and miscellaneous uses (11.5%) (Anon., 1977f)

During 1976 more than 1 billion pounds of ABS (dry weight basis) were produced in the U.S., up 33% from 1975 (U.S. Int. Trade Comm., 1975 and 1976). SAN production was about 121 million pounds (dry weight basis) during 1975, up 9% from 1974 (no 1976 data available; U.S. Int. Trade Comm., 1974, 1975, 1976). There are 9 manufacturers of ABS and/or SAN resins, as listed in Table 11.

c. Adiponitrile

About 10% of acrylonitrile demand is used in the manufacture of adiponitrile, an intermediate in the preparation of nylon 6,6. The process used by Monsanto (Decatur, Ala.) is the simultaneous dimerization and hydrogenation of acrylonitrile to form adiponitrile in an electrolytic cell. Other producers manufacture adiponitrile from butadiene (DuPont) or cyclohexane (Celanese, El Paso Natural Gas).

Table 11

Producers of ABS and SAN Resins[a] (SRI, 1977; Anon, 1977g; Anon, 1977h; Anon, 1977i; Anon, 1977j; Anon, 1978b)

	Capacity (millions of lbs.)	Product
Abtec Chemical Co.[b] Louisville, Ky.	65	ABS planning expansion
Borg-Warner Corp. Plastics		will add 120-150 million lbs in 1979
Ottawa, Ill.	215	ABS
Washington, W. Va.	300	ABS
Dart Indust. Inc. Rexene Polymers Co. Joliet, Ill.	60	ABS
Dow Chemical U.S.A.		
Gales Ferry, Conn.	65	ABS
Midland, Mich.	70	
Pevely, Mo.	65	
Torrance, Calif.	30	will add 150 million lbs in Torrance and at Hanging Rock, Ohio
Foster Grant Co., Inc. Leominister, Mass.	n/a	Pilot program
Grace Co. Owensboro, Ky.	-	ABS
Monsanto Co. Monsanto Polymers & Petrochemical Co. Addyston, Ohio	320	ABS (Lustran) likely to add 50 million lbs/yr late 1978
Muscatine, Iowa	125	ABS (Lustran)
Springfield, Mass.		
Rexene Styretics Joliet, Ill.	55	ABS

Table 11 (continued)

Producers of ABS and SAN Resins[a] (SRI, 1977; Anon, 1977g; Anon, 1977h; Anon, 1977i; Anon, 1977j; Anon, 1978b)

	Capacity (millions of lbs.)	Producer
Union Carbide Corp. Chemicals and Plastics Div. Bound Brook, N. J.	[30]	SAN; no longer producing SAN after 6/77
Uniroyal, Inc. Baton Rouge, La. Scotts Bluff, La.	200	ABS (Kralastic , Acrylon); expansion to 250 million lbs/yr likely

---

[a] some capacity figures include ABS and SAN; SAN capacity is considered proprietary

[b] joint venture of Cosden Oil and Chemical Co. and B. F. Goodrich Chemical Co.

d. Nitrile Rubber

Nitrile rubber (NBR) is formed by copolymerizing acrylonitrile and butadiene, with the proportions varying from 55:45 butadiene:acrylonitrile to 82:18 butadiene:acrylonitrile (Barnhart, 1968). The higher the proportion of acrylonitrile the higher the oil and gas resistance of the rubber. Acrylonitrile, butadiene, water, emulsifier, modifier and polymerization initiator system are added to a pressurized polymerizer. After polymerization the latex (which is usually steam stripped to remove unreacted butadiene and acrylonitrile) is allowed to coagulate, and washed to remove salts and emulsifiers (B. F. Goodrich, 1977). Since nitrile rubber does not swell or distort when exposed to oil and gas, it is widely used in products likely to contact petroleum products. End uses of NBR include hoses (31%), seals/gaskets/O-rings (17%), molded goods (11%), adhesives/sealants (9%), coated fabrics (8%), plastics-blends (6%), rubber covered rolls (5%), footwear (5%), and miscellaneous (8%) (Idol, 1974).

Production of NBR during 1976 was in excess of 165 million pounds, about 20% lower than production in 1973 and 1974 (U.S. Int. Trade Comm. 1973-1976); this decline is partly attributed to the rubber strike of 1976. The major manufacturers, their capacities and trade names for their nitrile rubber appear in Table 12.

e. Exports

More than 232 million pounds of acrylonitrile were exported from the U.S. during 1976, primarily to Latin America (47%), Canada (20%) and Western Europe (29%) (U.S. Bureau of Census, 1976b). Although imports have increased steadily since 1972 (Table 13), exports during 1976 did not reach the high levels of 1969 and 1970 (275×10^6 lb/yr; Anon, 1977c).

Table 12

Producers of Polybutadiene - AN Elastomers (NBR)
(SRI, 1975)

	Capacity (millions of lbs.)	Tradename
Copolymer Rubber and Chem. Corp.	11	Ny Syn
Baton Rouge, La.		
Firestone Tire and Rubber Co.	11	FR-N
Synthetic Rubber and Latex Div.		
Akron, Ohio		
B. F. Goodrich Co.		
Akron, Ohio	31	Hycar
Louisville, Ky.	62	Hycar
Goodyear Tire and Rubber Co.		
Akron, Ohio	11	Chemigum
Houston, Tex.	24	Chemigum
W. R. Grace and Co.	(a)	
Indust. Chems. Group		
South Acton, Mass.		
Standard Brands, Inc.	-	
Cheswold, Del.		
Uniroyal, Inc.		
Baton Rouge, La.	31	Paracril
Painesville, Ohio	31	Paracril

[a] not currently producing NBR

Table 13

Export Data for U.S. Acrylonitrile (U.S. Bureau of Census, 1972-1976)

Exported AN	1976	1975	1974	1973	1972[a]
Total Quantity (lb.)	232,929,957	197,882,730	154,224,384	105,331,222	51,845,988
Total Value ($)	51,050,530	43,966,987	37,214,924	12,455,899	5,458,233
Where Exported (%)[b]					
Western Hemisphere					
Canada	19.7	18.3	31.8	37.8	14.5
Latin America	46.9	32.7	40.5	38.5	66.2
Other	-	1.1	-	-	-
Western Europe	28.9	30.5	25.4	23.4	19.1
Communist Areas in Europe	-	-	1.3	-	-
Asia					
Japan	0.5	5.0	0.1	<0.1	<0.1
Other Asia	3.1	11.8	<0.1	0.1	<0.1
Australia	0.9	0.6	0.7	-	0.2
Africa	-	-	0.2	0.2	<0.1

[a] no data listed prior to 1972 in this source

[b] calculated as a percent of total quantity exported

f. Miscellaneous Uses

Acrylonitrile is used to produce acrylamide and barrier resins and as a fumigant. It is the major starting material for the manufacture of acrylamide. A widely used method of production involves direct hydration of acrylonitrile to produce high yields of acrylamide (Anon., 1973).

Acrylamides have application in water treatment (clarification and treatment of effluents, food etc.), paper chemistry (dry strength agents, retention aids, drainage aids), oil-well stimulation (fracturing, flooding), mineral processing (flocculation of ores, tailings, coal etc.) and soil stabilization, as well as other miscellaneous applications (Bikales, 1973).

There are currently three producers of acrylamide: American Cyanamid (Linden, N.J. and New Orleans, La.), Dow Chemical Co. (Midland, Mich.) and Nalco Chemical (Chicago, Ill.).

Another use of acrylonitrile is for nitrile barrier resin containers. Nitrile beverage bottles might have consumed 10% of the 1980 market for acrylonitrile (Anon., 1977c) had the Food and Drug Administration not banned its use Sept. 23, 1977 (Kennedy, 1977).

Nitrile barrier resins also have application in non-beverage packaging, including containers for glue, nail polish (Max Factor), correction fluid (Liquid Paper Corp.), air freshener (Airwick Industries) and for a contact lens disinfectant (Flexol). A new application is in the production of blister packages currently used for toothbrushes and combs (Anon., 1977k).

A small amount of acrylonitrile is used as a fumigant against insects and nematodes. It has been used particularly as a grain fumigant. In Florida, acrylonitrile has been used as a structural pesticide against dry wood termites, power post beetles and wood borers (Davis et al., 1973). Carbon tetrachloride is usually mixed with equal parts of acrylonitrile to reduce the flammability of the fumigant. Fumigant mixtures with methylene chloride trichloroacetonitrile, methyl bromide and also urea and ammonium sulfate have been described (Standish, 1974; Bond and Buckland, 1976).

A small use of acrylonitrile is in the cyanoethylation of natural fibers to improve heat and rot resistance. Another is for the manufacture of a thermoplastic with a high dielectric constant (Cyanocel manufactured by American Cyanamid) (Norris, 1967). Another use of acrylonitrile is as an anti-stall additive (Dow Ambifal 200).

Acrylonitrile is also used as an intermediate in the production of specialty chemicals, such as:

dimethylaminopropylamine
diethylaminopropylamine
monomethylaminopropylamine
polyglycoldiamine H 221
polyglycolamine
dimethylaminopropionitrile

(A.T. Kearney, Inc., 1978).

2. Projected Uses

The use categories discussed in the last section are projected to continue. Figure 3 compares acrylonitrile demand for fibers, resins, elastomers, exports and others during 1976 to the projected demand in 1980. New forms of acrylic fibers may contribute to the modest growth (5%) of acrylic fibers projected for the next few years (Anon., 1977c). ABS and SAN resins are expected to be leaders in the long-term growth of acrylonitrile (Anon., 1977b). Relatively slow growth is anticipated for nitrile elastomers, but use in acrylamide may increase substantially (Anon., 1977c).

3. Alternatives to Use

Major use categories of acrylonitrile include fibers, elastomers and resins for which substitute products exist. For example, other synthetic (ex. acetate, polyester, nylon) or natural (cotton, wool) fibers could be used. Instead of acrylonitrile elastomers, natural rubbers or synthetic elastomers (polyisobutene and butyl rubber, neoprene, butadiene, isoprene) might be utilized. ABS/SAN resins may be replaced by styrene-butadiene (SBR), polystyrene, or styrene-divinyl benzene. However, some companies have claimed there is no direct substitute for AN-based plastics as AN imparts very specific qualities to these products, particularly chemical resistance.

C. Entry into the Environment

Acrylonitrile monomer can enter the environment during its production, waste handling, storage, transfer, transport and end-use. Little data are currently available on levels of acrylonitrile in the environment. Information to supplement this section, however, will be available in the near future. The Midwest Research Institute (MRI) is presently taking air, water and soil samples at and near AN producer and user facilities for the Environmental Protection Agency (Office of Toxic Substances). In addition, studies are underway at the EPA Pollutant Strategies Branch to assess atmospheric hydrocarbons; data on AN may be gathered.

Table 14

Emission Factors for Acrylonitrile Manufacture (uncontrolled emissions; Hughes and Horn, 1977[a])

Material emitted	Amount[b] (g/kg of AN produced)
Carbon Monoxide [c]	79.30
Hydrocarbons (as CH_4)	71.06
Nitrogen Oxides	0.55
Sulfur Oxides	0.18
Methane	0.67
Ethane	1.93
Ethylene	2.57
Propane and Propylene [c]	55.02
Butene	0.40
Benzene [c]	0.15
Toluene [c]	0.07
Acrylonitrile[c]	0.89
Acetonitrile[c]	0.63
Hydrogen Cyanide[c]	0.66
Fumaronitrile	0.04
Pyridine[c]	5.2
Propionaldehyde	0.01
Furan	0.47
Ammonia	0.00
Allyl Alcohol	0.02

---

[a] a "representative acrylonitrile plant"; SOHIO process of 140,000 metric ton/year capacity located in a community with a population density of 402 persons/km^2.

[b] data for several emission points were obtained for each material; some data in reference are given to more significant figures than reported here.

[c] Vistron (1978) has measured somewhat different values at their production sites, as follows (in g/kg): CO - 121 to 146; propane and propylene - 57-71; no benzene or toluene; AN - 0.58-2.1; acetonitrile - 0.1-0.25; HCN - 0.1-0.25; pyridine - 0.5.

represents only a small part (0.4%) of total uncontrolled emissions from AN production (Table 14; data from Hughes and Horn, 1977). These emissions have been the subject of three studies (Patterson et al., 1976; Schwartz et al., 1975; Hughes and Horn, 1977) to which the reader is referred for more detail.

As discussed in Section I-A-1, acrylonitrile is manufactured by the ammoxidation of propylene. The simplified flow diagram in Figure 2 identifies product flow from reactor, to quencher, to absorber to recovery columns with resultant wastewater stream, by-product flare and incineration. Acrylonitrile emissions can result during several phases of this production process. Estimates for a "representative" acrylonitrile plant (Hughes and Horn, 1977) and for an actual production facility (Vistron, 1978) are given in Table 15. Preliminary information received by the EPA from acrylonitrile manufacturers indicate that the Hughes and Horn figures for absorber vent, fugitive emissions and storage may be underestimated. This preliminary information indicates that the amount of AN emitted to the atmosphere during acrylonitrile production is about 1/5 or 1/6 the amount of AN emitted during polymer operations; estimates for polymer operations are at least 4100 tons AN/year (Mascone, 1978).

Table 15

Sources of Atmospheric Contamination of Acrylonitrile[a] during Acrylonitrile Manufacture and Bulk Storage

Emission Point	Quantity AN emitted (g/kg AN produced)	
	Hughes & Horn, 1977[a]	Vistron, 1978[b]
Absorber Vent	0.039 (± 41%)[d]	0.02-0.74
Incinerator Stack	<0.0015	-
Flare Stack	0.039	-
Deep Well Pond	-[c]	-
Fugitive Emissions	0.00042 (± 20%)[d]	-
Product Transport		
Loading Facility	0.0065 (± 20%)[d]	0.5
Storage Tanks	0.802 (± 20%)	0.45
Total Average	0.888	

---

[a] applies to plants not controlling emissions; if emissions are controlled, absorber vent is source of <0.002 g/kg AN

[b] measured by Engineering Department at Vistron

[c] AN is about 0.02% of the wastewater column stream coming from the wastewater column bottoms

[d] figure may be higher according to EPA; see text

2. From Waste Handling

During acrylonitrile production the following wastes are produced: gaseous wastes, liquid wastes (wastewater column bottoms, acetonitrile column bottoms, heavy ends, crude acetonitrile, hydrogen cyanide) and solid wastes (catalyst fines and organic polymers). Three types of on-site disposal methods are used: 1) flare, 2) thermal incinceration and 3) deep well pond and deep well injection (Hughes and Horn, 1977).

The wastewater column stream coming from the wastewater column bottoms (stream 11) may contain 500 mg/l or less of acrylonitrile (but higher levels of CN^-, sulfate, NH_3 and acetonitrile) (Lowenbach et al., 1978). This wastewater is mixed with wastewater from the acetonitrile column (AN not identified as a component) and then sent to the deep well pond where solids are separated out. The liquid runoff is disposed of by deep well injection (Hughes and Horn, 1977, Fitzgibbons et al. 1973) (Figure 2). These wells are isolated from the groundwater. The possibility of contamination of groundwater from deep wells is remote (Lowenbach et al., 1978).[a] According to Vistron (1978) 590 gallons of wastewater are deep well injected per 1,000 pounds of AN produced; this water contains about 175 ppm AN. They also reported 130 gallons of wastewater/1,000 pounds AN produced are sent to a biopond; of this, AN is present at 120 ppm.

---

[a] The EPA no longer considers deep well injection a "viable" disposal method (Fed. Reg. Jan. 6, 1977). To control the drilling of new wells, industrial dischargers must re-apply for a permit under the National Pollution Discharge Elimination System (NPDES). Also, permit holders are required to submit summaries of current practices and practicable alternatives (Lowenbach, et al., 1978).

3. From Storage

As depicted in Figure 2, crude and purified acrylonitrile are stored prior to transportation in fixed roof storage tanks. Estimates for storage losses range from 0.45 (Vistron, 1978) to 0.802 (Hughes and Horn, 1977) g AN/kg AN produced. Losses during loading operations have been placed at 0.0065 and 0.5 g/kg by Hughes and Horn and by Vistron, respectively.

4. From Transportation

Acrylonitrile is shipped primarily by tank cars (40.4%), tank trucks (56.5%) and barge (1.7%) (OHM/TADS, n.d.). The following unlined containers are used: pails (5 gallon; 18 gauge black steel), drums (55 gallon; 18 gauge black steel), tank trucks (4,000-7,000 gal; carbon steel or aluminum) or tank cars (8,000-40,000 gallon; carbon steel or aluminum). The truckload minimum for drum shipments is 67 drums (24,000 lbs.) while the carload minimum is 84 drums (30,000 lbs.) (American Cyanamid, 1974, Vistron, 1978).

Spills of acrylonitrile can potentially enter any environmental medium. For example, the Intergovernmental Maritime Consultative Organization estimated 41 tons of acrylonitrile were discharged into the sea from transport and handling in 1970 (Nat'l. Acad. Sci., 1975). Spills occurring on land enter soil and groundwater.

In 1974 the Arthur D. Little Co., Inc. analyzed safety aspects of tank car, tank truck and barge transport for acrylonitrile shipped from Chocolate Bayou, Texas (AN produced) to Decatur, Alabama (AN used in fibers).

By barge, this route covers 1,400 miles, by rail, 770 miles and by truck, 780 miles. The total shipment considered was 80,000 tons/year. Based on (1) past accident rates, (2) the number of trips made by each mode, and (3) other factors, the following estimates were made of the annual number of accidents causing release of cargo: barge, 0.0117; truck, 0.063; and rail, 0.17. These figures represent the case where the entire commodity is transported by one mode. Taking this same model further, A. D. Little, Inc., in 1974 also estimated the spill pool radius, hazard radius, population exposure, probability of ignition and amount of property damage. These estimates appear in Table 16 and are based on flammability and water toxicity hazards. Transportation by rail is most hazardous and by barge, least hazardous for these parameters. By rail, spills are likely to occur more frequently, damage more property, and expose more individuals.

It should be noted that this model is based on the shipment of 80,000 tons/yr between two specified destinations. In actual practice, more than 300,000 tons of acrylonitrile were sold in the U.S. during 1976 (Table 4) and most was presumably shipped to the major use sites (Section II-B) located throughout the U.S. Captive consumption also involves some transport. Precise information on current transportation patterns for acrylonitrile, which would be necessary to assess total risk, is not available. Some data do exist, however, on actual acrylonitrile spills reported to the Oil and Hazardous Materials Spill Information Retrieval System of the Environmental Protection Agency (OHM-SIRS). OHM-SIRS cautions that only a small fraction (10-20%) of all spills are ever reported. From August 1970 to July 1975 12 acrylonitrile spills were reported, 10 of these

Table 16

Hazards of Acrylonitrile Transportation
(A.D. Little, Inc., 1974)

ACRYLONITRILE - Flammability + Water Toxicity Hazard(1)

	BARGE	TRUCK	RAIL
Spill Pool Radius (Feet)	200	56	104
Hazard Radius (Feet)	400	126	224
Hazard Area (Acres)	11.53(2) 1.35(4)	1.1(3)	3.3(3)
Relative Exposure (%) Urban/Rural	8/92	23/77	27/73
Expected Number of Annual Spills	.0117	.063	.17
Probability of Ignition Following Spill	.30	.25	.40
Expected Annual Number of People Exposed(5) Urban/Rural	.008/.004	.010/.002	.16/.016
Expected Annual Property Damage $(5) Urban/Rural	129/55	160/20	2423/252
Recurrence Interval(6) (Years)	85.5	15.8	5.8

[1] Calculations are based upon the assumption that each mode of transportation handles 100 percent of the quantity shipped.

[2] Area affected by spills into water which ignite. Assumes entire spill quantity contributes to burning pool.

[3] Area affected by spills on land which ignite. If no ignition occurs, the exposed land area is equivalent to the pool spill area (πR^2 spill).

[4] For spills into water which do not ignite the water toxicity hazard distance (feet) measured downstream from spill location for a 500 feet wide, 10 feet deep river flowing at 2.3 feet per second. Assumes vertical dispersion rate at 1.0 feet per minute until uniform mixing is achieved

Table 16 (continued)

Hazards of Acrylonitrile Transportation
(A.D. Little, Inc., 1974)

---

throughout the entire depth of the river. Thereafter, plug flow is assumed with no synergistic or antagonistic reaction between the pollutant and the receiving body of water. For this situation the entire spill quantity contributes to water.

[5] Expected number of people exposed annually and property damage is based upon ignition of the flammable pool for both land and water based spills.

[6] Average number of years between accidents.

Table 17

Spill Data for Acrylonitrile (E.P.A. Oil and Hazardous Materials Spill Information Retrieval System)

Date	Location	Quantity/Source	Damage	Waters Affected	Company Responsible	Remarks
7/28/71	Beaumont, Tex.	630 gallons/barge	unknown	DuPont Docks	Union Carbide Co.	-
10/27/71	Washington, W. Va.	/storage tank	unknown	Ohio River	Marbon Chemical Co.	-
1/20/72	North of Richmond, Va.	/truck	small fish kill	tributary to N. N. Anna River	Glosen Motor Lines	-
5/14/72	W. Lafayette,	/RR cars	P_2S_5 burned	-	Penn Central	also spilled: phosphorus, pentasulfide, vinyl chloride
10/8/72	River Mile 214	35 gallons/barge went aground	unknown	Tennessee River	Inland Oil Transportation Co.	-
10/30/73	Rush, Ky.	80,000 gal/tank car derailment and rupture	large fish kill	Little Sandy & tributaries	C & O RR	evacuation of area
11/1/73	Rantoul, Ill.	8,000 lbs/leaking valve in tank car	-	-	Illinois Central RR	leak absorbed by ballast
12/23/73	Mapleton, Ill.	35 tons/tank car derailment and tank rupture	soaked into soil	-	Toledo, Peoria, & W. RR	-
1/17/74	Austin, Ohio	unknown/derailment	-	-	B & O RR	-

Table 17 (continued)

Spill Data for Acrylonitrile (E.P.A. Oil and Hazardous Materials Spill Information Retrieval System)

Date	Location	Quantity/Source	Damage	Waters Affected	Company Responsible	Remarks
2/23/74	Vandalia, Ohio	48,000 lbs/plant pump malfunction	-	Poplar Creek	General Motors	-
11/19/74	Mansey, S.C.	10 gallons/tank car	-	-	Seaboard Coastline RR	-
/74	Dayton, Ohio	21,000 gallons/derailment	-	inland bayou	Texas Solvents Chem. Co.	-

occurring during transport (Table 17). Of these 10 spills, 7 occurred from tank cars, 2 from barges and 1 from a tank truck.

5. From End-Use

Environmental contamination from acrylonitrile is also possible through end product manufacture and use, resulting in low-level exposure to the general population. Preliminary information received by the EPA from AN users indicate that at least 4,100 tons AN are emitted yearly during polymerization operations per year (Mascone, 1978).

Another source of environmental contamination is from residual monomer in end products; examples are listed below:

Product-Name	ppm residual AN	Source
Kralastic & Paracril polymers	50	Uniroyal, Inc., 1977
Polywet polymer	<20	Uniroyal, Inc., 1977
UCAR-380 latex	250	Union Carbide Corp., 1977
UCAR-4358 latex	750	Union Carbide Corp., 1977
NIAX Polymer Polyols	100-300	Union Carbide Corp., 1977
Acrylic and Modacrylic fibers	∿ 0[a]	Dow Badische Co. 1977
Acrylamide monomer	50-100	American Cyanamid Co., 1977
Polyacrylamide	1	Kearney, 1978
Crude XT monomer	40-50	American Cyanamid Co., 1977
Acrylic fiber	< 1	American Cyanamid Co., 1977
Hycar rubber	0-100	B. F. Goodrich, 1977

[a] limit of detection 1 ppm

According to OSHA, levels of AN in fibers are so low that handling of the fibers is not a likely source of acrylonitrile exposure (Bingham, 1978).

In order for acrylonitrile to be released, the product must be heated (which would spoil the product); but even this would not result in a "significant exposure situation". Possibly, acrylonitrile might be leached from fabrics during laundering (EPA, 1977), although there have been no studies in this area.

A. T. Kearney Inc. (1978) assessed the residual acrylonitrile content of consumer products. Based primarily on data from manufacturers, A. T. Kearney concluded that acrylonitrile contained in acrylic or modacrylic fabric and in nonfood-contact ABS/SAN products will not migrate under normal use. Sufficient information on acrylonitrile in nitrile rubber latexes was not available.

A possible source of acrylonitrile contamination is from acrylamide products. For example, acrylonitrile might leach into aquatic systems from acrylamide during use in water treatment (EPA, 1977). Acrylamide is used as a soil consolidating agent; the presence of acrylonitrile as a volatile component of this agent was confirmed by Matsumura and Arito (1975). Acrylamide was obtained from two Japanese manufacturers and the volatile components were analyzed by gas chromatography both before and after polymerization. Before acrylamide polymerization, acrylonitrile was contained up to 0.3 mg/ml as an impurity. After gelation of an acrylamide solution by polymerization with sand (the way acrylamide is used as a soil consolidating agent), acrylonitrile evaporated in air up to 4440 mg/m^3 at equilibrium. The purity of Japanese acrylamide was not given.

Acrylonitrile monomer is expected to migrate from barrier nitrile resins used as beverage containers. This use in beverage containers has been banned by the Food and Drug Administration (Kennedy, 1977), who maintains that acrylonitrile is an indirect food additive and has not been shown to be safe. The F.D.A. concluded "use of acrylonitrile monomer to fabricate acrylonitrile copolymer beverage containers may reasonably be expected, and in fact does result in acrylonitrile beverage containers becoming a component of.....foods." Early tests by Monsanto, a manufacturer of the nitrile resin, found a maximum of 39 ppm residual monomer (average of 15 ppm) in older bottles but a maximum of 5 ppm (average of 3.3 ppm) in the newer type bottle (Anon., 1977 1).

Residual acrylonitrile can also result from its use as a fumigant. Berck (1960) investigated acrylonitrile residues on shelled walnuts fumigated with Acrylon (34% AN, 66% CCl_4, v/v).[a] Walnuts were fumigated either at atmospheric pressure (3 or 6 ml Acrylon added; Table 18A) or at reduced pressure (vacuum-fumigation; 1.882 g Acrylon added; Table 18B). When walnuts were exposed to acrylon for 18 or 48 hours at atmospheric pressure, retention of acrylonitrile over 38 days generally was lower when a smaller shorter Acrylon dose was introduced and when the samples were aerated after exposure (Table 18A). For all exposure conditions, acrylonitrile (detected polarographically) ranged from 17.5-7.5 ppm 2 days and from 8.5-0.0 ppm 38 days after exposure.

Under vacuum-fumigation conditions, comparable data were obtained over

---

[a] also known as Acritet (Stauffer Chemical Co.)

Table 18

Acrylonitrile Residues in Walnuts
(Berck, 1960)

A. Amount of Acrylonitrile on Atmospheric-Fumigated Walnuts[a]

Acrylon added (ml)	Exposure (hr)	Fan (hr)	PPM Acrylonitrile, days after packaging[b]		
			2	18	38
3	48	4	7.5	0.0	2.5
3	48	0	10.0	0.8	2.0
6	48	4	10.0	2.5	3.7
6	48	0	17.5	6.8	8.5
3	18	4	5.0	0.0	0.0
3	18	0	6.0	0.0	0.5
6	18	4	11.0	2.4	1.0
6	18	0	13.5	4.1	5.0

[a] Acrylon introduced by syringe into 55 pound bags (polyethylene) of shelled walnuts. Walnuts were exposed for 18 or 48 hours, then spread out on a board; sometimes, this was followed by aeration in front of a fan. Samples were analyzed polarographically for AN on the days shown.

[b] original data presented for days 2, 9, 18, 24, 30, and 38.

B. Amount of Acrylonitrile on Vacuum-Fumigated Walnuts[a]

Acrylon added (g)	Exposure (hr)	Aeration (hr)	PPM Acrylonitrile, days after packaging[b]		
			1	14	30
1.882	3 at 110 mm Hg	0	16.6	6.8	1.3
1.882	3 at 110 mm Hg	16	12.5	2.5	0.0

[a] Air pressure was reduced before Acrylon was added; ten lbs (4.55 kg) of nuts were placed in a 24.1 liter vacuum-fumigating chamber; aeration followed exposure. Samples were analyzed polarographically.

[b] Original data presented for 0.75, 1, 4, 8, 14, 21, and 30 days.

30 days (Table 18B). It is difficult to compare results of the two exposure methods, as the initial doses and duration of exposure were different.

D. Disposal and Control Methods

1. Waste Disposal

The major treatment technology practiced at acrylonitrile manufacturing plants is direct discharge to deep wells. Subsurface disposal is used at all production sites except at duPont's plant in Memphis, Tennessee. Here, some of the wastes are pretreated by alkaline hydrolysis; then the biodegradable effluent is disposed of in publicly owned treatment works. In addition, a portion of the Memphis facility wasteload is incinerated (Lowenbach et al., 1978).

Deep well injection is no longer considered a viable disposal method and the development of alternate disposal systems appears inevitable. Lowenbach et al. (1978) extensively reviewed the available literature on alternate methods of treating wastewaters from acrylonitrile manufacture, including the following: biological treatment; chemical pretreatment (chemical oxidation and chemical precipitation); physical pretreatment (separation and ammonium sulfate recovery); and combination and alternative techniques (e.g., wet-oxidation with biophysical treatment). The reader is referred to Lowenbach et al. (1978), as a discussion of treatment alternatives is out of the scope of this report.

The Greater Peoria (Ill.) Sanitary District tested the potential effects of acrylonitrile on their wastewater treatment plants (Hughes, 1974). They evaluated whether to accept groundwater contaminated with acrylonitrile, as a result of a 20,000 gallon tank car spill (discussed in more detail in Section II-E). The Director of Waste Treatment Facilities reported inhibition of indicator microorganisms in the activated sludge system at concentrations of 120 mg AN/l. Complete inactivation occurred consistently at concentrations of 800 mg/l or more. However, acrylonitrile could be effectively treated when introduced into the treatment plant's aeration system at low concentrations. At concentrations of 40 mg AN/l or less, less than 1 mg/l was detected in the settled mixed liquor supernatant after 3 hours of aeration. At concentrations greater than 40 mg/l, concentrations as high as 20 mg/l remained after 3 hours of aeration.

Assimilation and digestion are discussed in more detail in Section II-E-1.

2. Control Technology

Emissions resulting from acrylonitrile manufacture occur mainly from the absorber vent, as previously discussed. All plants use a mist eliminator at the top of the absorber, but this only prevents liquid carryover to the atmosphere (Schwartz et al., 1975). Monsanto's acrylonitrile plants in Alvin, Texas and Texas City, Texas were using an effective emission control device (Hughes and Horn, 1977; Mascone, 1978). This device is a thermal oxidizer (incinerator) for by-product HCN and acetonitrile disposal and for vent gas control. The oxidizer removes more than 95% of carbon monoxide and total hydrocarbons. During 1976 DuPont's plant in Beaumont, Texas will have been controlled with a catalytic oxidizer. These changes resulted to meet emission levels for CO and hydrocarbons set by the Texas Air Control

Board (Hughes and Horn, 1977). Current research in industry for air pollution control involves primarily the development of a more selective catalyst to reduce by-products and increase ammonia utilization (Schwartz et al., 1975).

According to Hughes and Horn (1977) the largest single source of acrylonitrile emissions is from fixed roof storage tanks. One way to control these emissions is to install tanks with lower loss rates than fixed roof tanks, such as floating roof tanks, internal floating covers and vapor recovery systems. Another way to control emissions is to use retrofitable controls on existing fixed roof storage tanks such as internal floating roofs and vapor recovery systems (EPA, 1977).

E. Fate and Persistence in the Environment

In this section the degradation of acrylonitrile is reviewed and used to assess environmental persistence.

1. Degradation in the Environment

a. Biological Degradation

The environmental fate of acrylonitrile has not been extensively studied

(Nat'l. Acad. Sci., 1975). Limited data suggest that loss of small amounts of acrylonitrile from water systems can be expected to occur by biological degradation. Aerobic bacteria are capable of breaking down acrylonitrile, especially if already acclimated to this substance (Mills and Stack, 1955; Ludzack et al., 1958; Cherry et al., 1956). Breakdown products in aerobic aquatic systems may include ammonia and acrylic acid (Mills and Stack, 1955). Degradation of small amounts of acrylonitrile is also possible by acclimated anaerobic bacteria (Lank, 1969). Giacin et al. (1973) suggested terrestrial breakdown by soil fungi. Mills and Stack (1955) suggested a mechanism for the biological oxidation of acrylonitrile. Acrylonitrile was seeded with microorganisms from the Kanawha River (W.Va.), which had been acclimated to acrylonitrile for 27 days. The rate of biological oxidation was quite rapid (Figure 4), nearing completion in five days. The following nitrogen balance was obtained:

	Nitrogen Balance, as mg of N		
	Initial	Final	Changes
Nitrate and Nitrile	1.4	1.8	-
Ammonia	130	396	+266
Organic N	118	162	+ 44
		Total	310 mg N changed
		(388 mg N added initially)	

From these data the authors suggested that the biological oxidation of acrylonitrile proceeds by an enzyme-catalyzed hydrolysis of the nitrile group to acrylic acid and ammonia. Similarly, experiments at Dow Chemical Company indicate almost complete oxidation to ammonia 20 days after acrylonitrile was added to activated sludge seed (Nat'l. Acad. Sci., 1975).

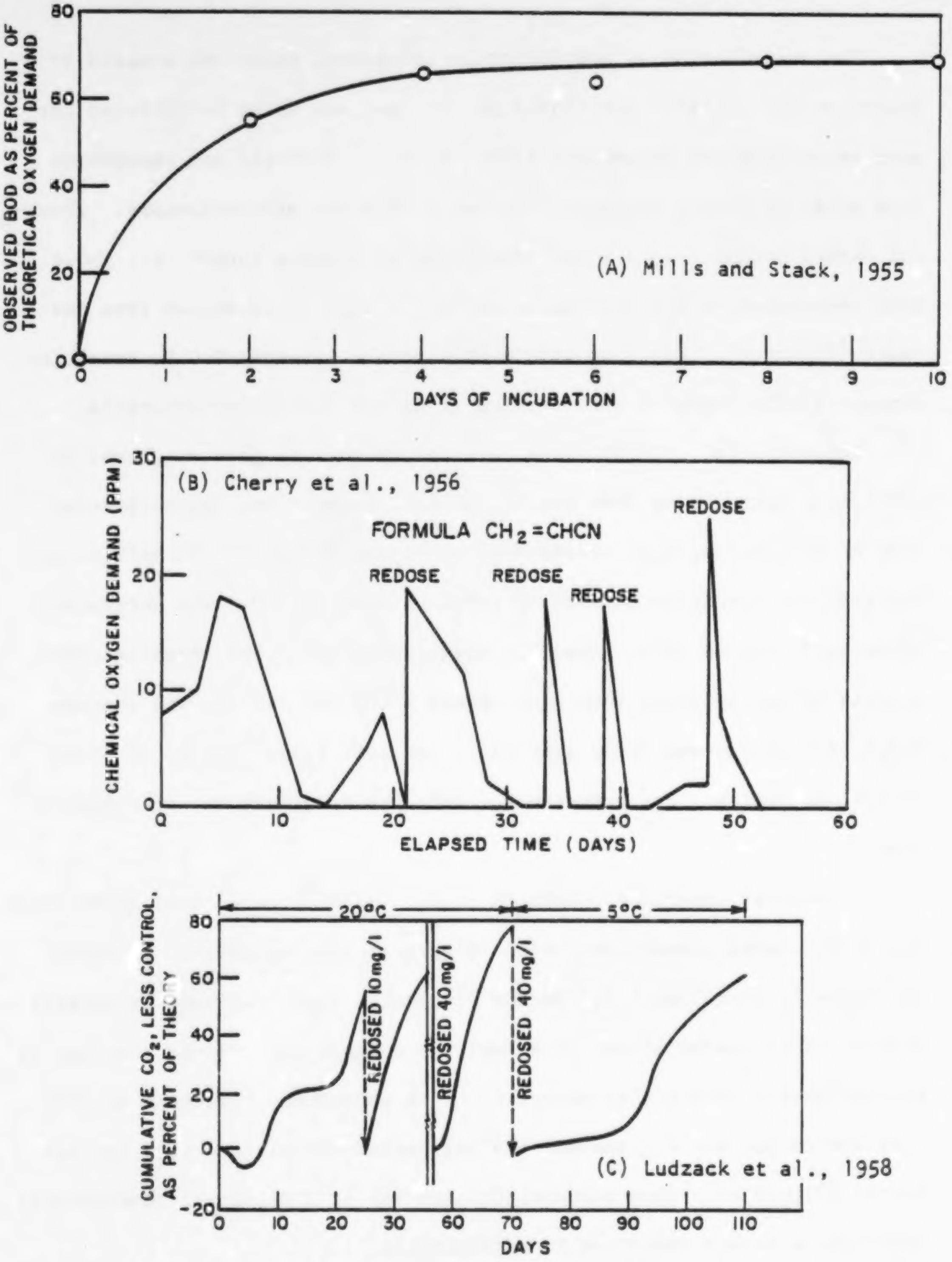


Figure 4. Biological Oxidation of Acrylonitrile in Aqueous Systems (See text for experimental conditions)

The assimilation of acrylonitrile in natural water was studied by Cherry et al. (1956). Acrylonitrile (10 ppm) was added to filtered aerated water from the Hackensack River (N. J.). Nitrogen and phosphorus were added to supply inorganic nutrients to river microorganisms. Chemical oxygen demand (C.O.D.) was determined at various intervals. About 20 days were required for acrylonitrile (at 10 ppm) to disappear from the water (Figure 4). Redosing with acrylonitrile lessened C.O.D. reduction times. Similar results were obtaind at 25 and 50 ppm acrylonitrile.

Ludzack et al. (1958) found acrylonitrile to be more resistant to biological degradation than aceto-, adipo-, benzo-, and lacto-nitriles. Ohio River water or aged sewage seed was treated with 0.1-20 mg/l acrylonitrile; the resulting biological oxygen demand (B.O.D.) was determined after 2, 5, and 12 days. The Ohio River water contained organisms more capable of assimilation than aged sewage seed: on day 15, the average B.O.D. for sewage and river seed was 5 and 15%, respectively, of theoretical oxidation. For both seeds, there was no oxidation after just 5 days.

In another experiment, Ludzack et al. (1958) treated Ohio River water (at 20°C, summer temperature) with 10 mg/l of acrylonitrile. As shown in Figure 4, there was a lag period of about a week, followed by several days of rapid assimilation, after which a plateau was reached. By day 22 another period of activity occurred. Upon subsequent treatment at 20°C (the system was now acclimated) the lag period and plateau were not detected (Figure 4). When readministration was at 5°C (winter temperature) there was a marked reduction in assimilation.

Kato and Yamamura (1976) identified aerobic microorganisms of the genus *Nocardia* as capable of degrading cyanides and nitrile.

The preceding studies show that breakdown of acrylonitrile can occur aerobically. Ludzack et al. (1959), Lank (1969) and Hovious et al. (1973) studied acrylonitrile under anaerobic conditions.

Lank (1969) found that acrylonitrile at a concentration of 10 mg/1 could be treated by anaerobic digestion. Two digesters were used. One digester fed only raw sludge served as the control; a second was given acrylonitrile continuously (1, 2, 4 or 10 mg/1) and sludge. Analyses to evaluate digester performance included volatile solid reduction, chemical oxygen demand reduction, volatile acid concentration and gas production. Control and experimental digester performance did not differ.

Although Lank (1969) found small amounts of acrylonitrile can be treated anaerobically, Hovious et al. (1973) determined that higher levels of acrylonitrile are inhibitory to some anaerobes. They tested the influence of acrylonitrile on the anaerobic activity of methanogenic bacteria which metabolize acetate. A Warburg respirometer was used to compare bacterial gas production in control (no acrylonitrile) and experimental (50-1,000 mg AN/1) flasks containing unacclimated anaerobic biomass. An activity ratio was calculated for each experimental concentration tested, which compares the slopes of the gas produced. An activity ratio of 1.0 indicates no effect, while a ratio less than 1.0 indicates inhibition of bacterial fermentation. Two separate series of experiments were carried out: a) food-limited substrate (no acetate added) and b) non-limited substrate (500 mg/1 acetate added per Warburg flask).

Inhibition was observed at all concentrations tested (50 to 1,000 mg AN/1) but was most severe at the highest concentration (Table 19).

Table 19

Effect of Acrylonitrile on Anaerobic Activity
(Hovious et al., 1973)

AN Concentration (mg/l)	Activity Ratio[a]	
	Non-limited Substrate	Substrate Limited
0	1	-[b]
50	0.6	-
100	0.5	0.6
200	-	0.42
300	0.4	-
500	-	0.38
1,000	0.3	-

[a] data from Fig. 10 of Hovious et al., 1973 [b] line indicates no testing

Although inhibition was observed, there was still some residual activity. Activity ratios were not as low as when known toxicants (chloroform, mercuric chloride, hydrochloric acid) were tested; at 1000 mg/l doses of these known toxicants, activity ratios ranged from 0.17-0.19.

For terrestrial systems, acrylonitrile can be utilized by soil fungi as a source of nitrogen and carbon (Giacin et al., 1973). Fungi capable of acrylonitrile biodegradation include *Pencillium, Aspergillus* and *Cladosporium* species. Although other microorganisms slowly degraded acrylonitrile, best results were obtained with soil fungi.

The preceding discussion considered only papers dealing with the biological degradation of AN. This is not meant to imply that biological treatment of wastewater from AN manufacturing facilities is desirable or even possible. These streams contain a complex mixture of organic compounds, not just acrylonitrile (reviewed in Lowenbach et al., 1978).

b. Chemical Degradation

Information on industrial and laboratory reactions for acrylonitrile has been presented in Section I-D. Unfortunately, no controlled studies are available for reactions under environmental conditions. Based on physical properties, however, it is possible to predict the behavior of acrylonitrile. Acrylonitrile is a volatile compound; its high vapor pressure (Table 2) would suggest appreciable evaporation. Acrylonitrile is only moderately soluble in water at about 7%. Possible atmospheric and aquatic reactions are discussed below.

1) Atmospheric Reactions

Olefins, as a class, generally enhance atmospheric oxidation reactions (Seinfeld, 1975). Acrylonitrile, an olefin, might be expected to participate in these reactions. However, no specific references are available on the fate of acrylonitrile in the atmosphere, although acrylonitrile is present in the atmosphere near production sites (see Section II-C-1). The following brief discussion considers the oxidation of olefins by atomic oxygen, hydroxyl radicals and ozone.

Atomic Oxygen Oxidation (Seinfeld, 1975)

Oxygen atoms, which form in the atmosphere as a result of the photolysis of nitrogen dioxide, usually add to olefins. Oxygen atoms react with olefins more rapidly than with other hydrocarbons (i.e., aromatics, acetylene). This addition reaction forms on excited epoxide, which then decomposes to an alkyl and an acyl radical.

Hydroxyl Radical Oxidation

Hydroxyl radicals (OH·) form in the atmosphere as a result of the photolysis of nitrous acid and as degradation products of free radicals. Hydroxyl radicals add at the double bonds (Seinfeld, 1975).

Morris and Niki (1971) measured the reactivity of hydroxyl radicals with several olefins (but not with acrylonitrile). Their data show that for a given olefin, the rate constant for the hydroxyl-olefin reaction is about 10 times greater than for the atomic oxygen-olefin reaction.

Ozone Oxidation (Seinfeld, 1975)

Atmospheric ozone forms in significant quantities when NO_2 levels are about 25 times NO levels. Ozone, while not as strong an oxidizing agent as O or OH, reacts with olefins at "appreciable rates" when ozone concentrations reach 0.25 ppm or more (Seinfeld, 1975). Ozone adds across the olefin double bond forming an aldehyde and a diradical (or Zwitterion). The diradical might decompose or participate in reactions with O_2, NO_2 and NO.

2) Reaction with Water

Acrylonitrile does not react with water and is labeled 0 (no hazard) in the N.A.S. Hazard Rating System for reactivity with water (Department of Transportation, 1974). Hydrogen cyanide is not an expected breakdown product, as acrylonitrile does not dissociate appreciably in water (McKee and Wolf, 1963).

2. Transport Within and Between Media

As emphasized in the previous section, acrylonitrile is quite volatile. One would expect, for example, considerable evaporation from land and water (as in a spill situation) into the atmosphere.

A spill of 36,000 gallons of acrylonitrile onto farmland (Gilford, Inc., 2/22/77) caused contamination of the groundwater and a nearby creek after acrylonitrile percolated through frozen soil (Manganaro, pers. comm., 1977). A spill of 20,000 gallons of acrylonitrile (near Mapleton, Ill., 12/23/73) caused contamination of the groundwater and a creek located about 750 feet from the spill. Acrylonitrile percolated through clay soil and was detected in nearby monitoring wells almost a year later and in the creek after about 100 days (Table 20, data provided by the Illinois EPA).

3. Persistence and Bioaccumulation

Because acrylonitrile is reactive and subject to bacterial degradation, loss is expected from environmental media. However, since acrylonitrile is toxic to most organisms at low concentrations (see Section III) these high initial levels may not be tolerated. No food chain concentration potential has been noted (Dept. of Transportation, 1974).

No experimental studies on the persistence of acrylonitrile are available. Data from the Gilford Spill (see previous section) indicate at least some short-term persistence. For several months after the spill, the concentration of acrylonitrile in the groundwater increased after it rained (Manganaro, 1977). Presumably, rainwater caused acrylonitrile to percolate through the soil. Importantly, acrylonitrile must have persisted in the soil (no quantitative measurements of the soil concentrations were made); microbial breakdown may have been retarded by the freezing temperatures.

Data provided by the Illinois Environmental Protection (Table 20) showed that acrylonitrile persisted for about a year or more in monitoring wells located near a tank car spill of 20,000 gallons of AN. No attempt was made by the railroad to contain or clean up the spill until 108 days after the spill occurred. Monitoring data from wells showed high levels of acrylonitrile until that time (3520-46 mg/l in 5 wells located within 100 feet of the spill). On day 108, about 270 cubic yards of contaminated

Table 20

Concentration of AN (mg/l) at Sampling Sites After Tank Car Spill of 20,000 Gallons on 12/23/73 near Mapleton, Ill.[a]

		Monitoring Well							Little Marsh Creek		
		1	2	3	4	5	6	11	A	B	C
Distance from Spill (ft):		88	73	73	73	94	324	600	900	750	3,000
Date (1974)	Days Since Spill										
1/4	13	8	1,150	4,200	35,000	–	–	–	–	–	–
1/9	18	330	240	3,900	35,000	–	–	–	–	–	–
1/14	23	1,200	370	4,200	23,000	–	–	–	–	–	–
1/16	25	2,100	430	6,000	18,000	400	0	–	–	–	–
1/17	26	2,700	470	6,000	15,000	400	2	0	–	–	–
1/21	30	2,100	2,000	8,800	12,000	10,500	7	0	–	–	–
2/27	58	14	370	6,500	1,600	4,200	3	–	0	32	8
3/18	77	6	180	5,400	540	2,100	2	0	0	3	5
3/28	87	6	120	4,400	980	1,980	2	–	0	3	5
4/8	98	46	97	3,520	418	2,020	0	0	0	2.6	5.6
4/18	108	0	282	3,070	174	1,240	0	0	0	0	0
5/1	121	0	1,100	3,260	146	1,340	–	–	0	0	0
5/15	135	3	1,100	3,560	< 1	901	–	–	0	0	0
6/20	171	469	1,220	2,420	1.4	150	–	–	0	0	0
8/15	227	90	1,028	771	0	157	–	–	0	0	0
9/4	247	40	40	1,200	40	25	–	–	–	–	–
9/17	260	0	4	–	40	0	–	–	–	–	–
12/9	351	0	0	1,020	–	0	–	–	–	–	–

---

[a] data provided by Illinois Environmental Protection Agency and contained in a series of letters. Nine additional wells, located 472-2140 feet ($\bar{x} \simeq 1000$ ft) from spill site, were sampled until about 4/8; AN levels were 0 mg/l. Tap water at 6 nearby residences (220-2120 ft. from site; $\bar{x} \simeq 1150$ ft) sampled throughout year and contained no AN

soil were removed. After this, levels of AN actually increased in some wells. Levels decreased after about 170 days when contaminated groundwater was pumped into a railroad car. A sample of this groundwater revealed 144 mg/l of acrylonitrile. About 10 months after the spill, the still-contaminated groundwater was pumped into a sewage treatment plant.

It is probable that the large volume of acrylonitrile from the spill was lethal to bacteria, precluding biological degradation. No quantitative measurements of soil or water organisms were made.

F. Hazards from Combustion

1. Thermal Degradation

Thermal degradation of acrylonitrile or polyacrylonitrile may result in the production of hydrogen cyanide, but the nature of volatile products depends somewhat on the temperature used (reviewed in Madorsky, 1964).

Bott et al. (1969) investigated the evolution of toxic gases during thermal decomposition of acrylonitrile in air and in nitrogen. Acrylonitrile was decomposed in a regulated furnace (± 5°) and the resulting gases were analyzed spectrophotometrically. Hydrogen cyanide and ammonia formed in both air and nitrogen.

At 500°C the following gases were produced in air:

	ppm
HCN	3000
CO	400
NH_3	7000
Oxides of N	25

The lowest temperature that hydrogen cyanide evolved in air was 250°C. CO, NH_3 and oxides evolved at 360-480°C. Bott et al. (1969) suggested that the rate of hydrogen cyanide evolution depends on the rate of breakage of chemical bonds adjacent to the cyanide group in acrylonitrile.

Thermal decomposition of polyacrylonitrile yields primarily hydrogen cyanide (Tsuchiya and Sumi, 1977). One gram samples of 100% polyacrylonitrile yarn were decomposed in a quartz tube heated to 400°, 600° or 800°C under a flow of nitrogen or air. Decomposition products were determined by gas chromatography and gas chromatography-mass spectrometry. Hydrogen cyanide was the major product under all decomposition conditions, the quantity increasing with temperature (e.g., in air at 400°C and 800°C, the weight of evolved HCN was 2.0% and 13.2%, respectively, of weight of original polymer). Acrylonitrile was the second predominant decomposition product, ranging from 0.15-18.3% in nitrogen and 0.99-6.26% in air and increasing with temperature. Smaller amounts of 15 other nitriles were identified.

Hydrogen cyanide is also the predominant product upon thermal degradation of acrylonitrile-styrene (AS) or acrylonitrile-butadiene-styrene (ABS) (Chaigneau and LeMoan, 1974). AS, ABS, and polyacrylonitrile (PAN) were pyrolyzed at 500 to 1200°C. Between 2.13-7.42, 3.00-7.61 and 1.86-16.2 g HCN, respectively, were released per 100 g of starting product, the amount depending on the temperature.

2. Mortality from Pyrolysis Products

Cornish et al. (1975) determined the mortality of thermal degradation products of styrene-acrylonitrile (SAN) and acrylonitrile-butadiene-styrene

(ABS) in male Sprague-Dawley rats (av. wt. 250 g). Two degradation methods were used: rapid combustion and slow pyrolysis. In the first method, groups of 15 rats were placed in a 1500 l stainless steel chamber. The polymers were quickly pyrolized and rats were exposed to the pyrolysis products (vapors and particulate matter) over 4 hours; several concentrations of the polymers were tested to determine approximate 0-100% mortality levels. For the slow pyrolysis method, groups of 5 rats were exposed to the pyrolysis products only during the time they were released from the polymer. Air in the pyrolysis chamber was cooled and diluted and entered a Pyrex exposure chamber housing the rats. Approximate 0-100% mortality levels were determined using several polymer concentrations.

These data were obtained for the two methods:

	0-100% mortality range[a] (g pyrolyzed product)	
Method	SAN	ABS
Rapid Combustion	10-28[b]	25-30
Slow Pyrolysis	1.0-2.5	1.5-2.3

[a] estimated from graphs in text

[b] 100% mortality had not been reached at 28 g

The constituents of the exposure atmosphere were not monitored, so relating these data to acrylonitrile toxicity is difficult.

The toxicity of the pyrolysis products of acrylonitrile-butadiene-styrene (ABS) was assessed by Hilado et al. (1976). Four Swiss albino mice were exposed to pyrolysis effluents (1 g ABS pyrolyzed at a maximum of 791°C) in a 4.2 liter chamber in each of 2 trials. At least one mouse became incapacitated about 11.35 ± 3.2 minutes after exposure, as evidenced by staggering, prostration, collapse, or convulsion. Death occurred after about 19.30 ± 4.25 minutes for all mice.

G. Analytical Detection Methods

Titrimetric, polarographic and especially gas chromatographic procedures are often used to determine acrylonitrile. Detection methods for several media will be described in the following sections.

1. In Air

A widely used procedure to determine the concentration of acrylonitrile in workroom air is the NIOSH method S156 (NIOSH, 1976). For example, this method is used by Monsanto, Sohio, and Borg-Warner, and a modification of this method is used by Union Carbide (Monsanto, 1977b; Sohio, 1977; Union Carbide, 1977; Borg-Warner, 1977). The procedure involves drawing a known volume of air (20 l maximum recommended) through a charcoal tube consisting of 2 sections to trap organic vapors. One sample of charcoal from each section is transferred to a separate container where each is desorbed for 30 minutes in methanol. An aliquot of each desorbed sample is analyzed by gas chromatography. The area of the resulting peak is determined and compared with standards based on mg/1.0 ml methanol; corrections must be made for the blank (NIOSH, 1976).

This method was originally validated by NIOSH over 17.5-70.0 mg/m^3 (8.1-32.3 ppm) (coefficient of variation 0.073) at 22°C and 760 mm Hg using a 20 liter sample. However, recent studies at OSHA indicate a sensitivity of 0.05 ppm based on an air volume of 10 liters. The collection efficiency was 100% when sampling at 0.1 lpm in the volume range of 12-25 liters. Additional studies were conducted in the presence of 10 or 100 ppm butadiene, methyl methacrylate and styrene. These three interferences had no effect on the collection efficiency of acrylonitrile (Madsen, 1978).

The Midwest Research Institute (M.R.I.) is currently sampling the air near AN producer and user facilities for the Environmental Protection Agency. Their method involves using charcoal tubes sampling at 1 l/min. The sample is desorbed with carbon disulfide and analyzed using a flame ionization detector.

Another method used for detecting acrylonitrile is the older NIOSH P&CAM 127 (1974) where the sample is desorbed with carbon disulfide (CS_2) rather than methanol. DuPont introduced a method where a CS_2-acetone mixture is the desorber. Acrylonitrile can also be measured with other adsorber-desorption systems. These methods are listed in Table 21 with their respective sensitivity, accuracy and interferences.

Direct measurement of acrylonitrile can be made using an infrared (I.R.) spectrometer, but according to Borg-Warner (1977) this apparatus costs more, requires more skill to use and is more sensitive to physical damage than the charcoal-tube method. Jacobs and Syrjala (in press, 1978) recommend portable I.R. analyzers for immediate "on-the-spot" detection of acrylonitrile. They claim detection of acrylonitrile as low as 0.2 ppm with MIRAN 1A Analyzer (20 meter cell; Foxboro/Wilks, Inc.). Interferences are other compounds that absorb infrared energy with a wavelength

Table 21

Methods for Determining Acrylonitrile in the Air

Method	Procedure	Sensitivity and Accuracy	Interferences	Reference
NIOSH, No. S156	absorbed on charcoal; desorbed with methanol[a]; G.C.[c]	0.05 ppm	primarily nitrogen containing compounds which elute at the same time as AN when using a nitrogen detector	NIOSH, 1976
DuPont Polymer Intermediates Dept., No. 5000	absorbed on charcoal; desorbed with carbon disulfide-acetone; G.C.	86.7% (S.D. = 54%) when 10 ppm AN sampled	any component not separated	Monsanto, 1977
DuPont Polymer Intermediates Dept., No. 5004	absorbed from known volume of air in chilled water; G.C.	lower unit 5 ppm AN per cubic foot of sample	any component not separated	Monsanto, 1977
NIOSH, No. 75-121, P&CAM 127	absorbed on charcoal; desorbed with carbon disulfide G.C.	not specified for acrylonitrile	water; any component not separated	NIOSH, 1974
Monsanto, No. IH 9 (TC)	adsorption on porous polymer; thermal desorption; G.C.	range 0.2-200 ppm[d]	acetone, isopropanol	Monsanto, 1977

[a] Union Carbide substitutes ethylene dichloride for methanol (Union Carbide, 1977)

[b] coefficient of variation

[c] G.C. = gas chromatography

[d] under laboratory, not field, conditions

of 10.5 μm (Jacobs and Syrjala, in press 1978). Another method used by Borg-Warner is a continuously recording gas chromatograph which reportedly detects acrylonitrile below 0.5 ppm (Borg-Warner, 1977). Union Carbide is experimenting with a badge-type, carbon-filled dosimeter for vapor collection, but tests are inconclusive. Direct-injection gas chromatography for acrylonitrile is being tested; preliminary results indicate detection below 1 ppm (Union Carbide, 1977). Vistron (1978) is also investigating the portable gas chromatograph and the badge-type carbon-filled disometer.

The American Industrial Hygiene Association (1970) suggested three methods for analyzing acrylonitrile in air: vapor phase chromatography, the infrared absorption method and the hydrolysis method. In the latter, air is drawn through two adsorbing glass bead traps that have been wetted with sulfuric acid. Acrylonitrile reacts with the sulfuric acid. The product is treated with hydrogen peroxide, which liberates the ammonium ion. The amount of the latter liberated (measured colorimetrically) is used to determine the amount of acrylonitrile in the air sample; sensitivity is in the range of 20-300 μg/ml of absorbing solution. The American Industrial Hygiene Association suggests infrared analysis and chromatography are more sensitive methods than hydrolysis.

Tada (1971) suggested using the brom-benzidine-pyridine method which can detect 1-50 ppm AN in the atmosphere. Air is aspirated through a bubbler containing cooled water. The solution is added to bromine, then exposed to light. Next, an arsenite and then benzene-pyridine solution are added. The absorbance of the resulting solution is read.

Older and less precise procedures for determining acrylonitrile in air include the lauryl mercaptan method (Haslam and Newlands, 1955) and the potassium permanganate method (Gisclard et al., 1958).

2. In Aqueous Solution

For analyses, acrylonitrile can be separated from water and from impurities in water by gas chromatography, then measured and compared to AN standards in water. The detection limit has been reported as 0.1 ppm by DuPont (1977b) and 50 ppb by Monsanto (Livingston, 1977).

In a sampling program for the Environmental Protection Agency, the Midwest Research Institute (M.R.I.) has developed a protocol for sampling water containing acrylonitrile (MRI, 1977). Water samples are collected then acidified by the addition of sulfuric acid. Two types of analysis are used: azeotropic distillation and purge and trap techniques. A modification of the purge and trap techniques can be used to analyze soil containing acrylonitrile.

Hall and Stevens (1977) developed a spectrophotometric method to detect acrylonitrile in aqueous systems, based on the absorbance of visible light (at 411 nm) of a pyridine-acrylonitrile complex. An aqueous sample containing acrylonitrile is added to solutions of pyridine, lithium hydroxide and sodium hypochlorite, after which absorbances are determined. Acrylonitrile forms a complex whose molar absorptivity is 635.4, based on the acrylonitrile concentration. Acetone and ammonia did not interfere at the 10 or 100 ppm level. Cyanide interferes and must be separated out of solution; it is easily detected. The range of sample used by the authors was 5-30 ppm (S.D. = ± 3.18%) of acrylonitrile.

3. In By-Products

Residual acrylonitrile monomer in polymer by-products can be determined by gas chromatography, either by direct injection or by head-space analysis. Steichen (1976) compared the two methods for acrylonitrile and found head-space analysis to be more sensitive (detection limit 0.5 ppm) than direct injection (detection limit 10 ppm). Head-space analysis involves the equilibration of a solid polymer in a closed system. The residual monomer is partitioned between the polymer phase and the head-space (air above the sample); the monomer concentration in the head-space is then determined (Steichen, 1976).

The Food and Drug Administration is using a head-space method to determine AN in food simulating solvents (heptane; 3% acetic acid; 8 and 50% ethanol) that have been in contact with AN copolymers. AN (0.04-10 ppm) was measured by gas chromatography with a nitrogen selective detector (FDA,1977).

Monsanto developed a method for extracting residual acrylonitrile in acrylic polymer and fiber by heating above its glass transition temperature under a total water reflux. The extract is distilled, then analyzed by high pressure liquid chromatography. No interferences have been noted. To determine AN in SAN-based polymers, Monsanto disperses the polymer in acetone. The acetone is analyzed by gas chromatography using a nitrogen detector (unpublished methods presented in A. T. Kearney, Inc., 1978).

4. In Fumigated Food

Residues of acrylonitrile, arising out of its use (often with carbon tetrachloride) as a fumigant, can be detected by several methods. Heuser and Scudmore (1968) described a procedure for extracting residual acrylonitrile by static cold solvent extraction and gas-liquid chromatography. Total recovery of 99.1-100.2% was reported.

Berck (1960) used a polarographic method to determine acrylonitrile residues on walnuts. This method is based on the fact that acrylonitrile forms an azeotropic mixture with water and therefore can be concentrated and codistilled out of aqueous suspensions. Ninety five to 100% of the total acrylonitrile was recovered.

Acrylonitrile residues have also been determined by the lauryl mercaptan method and by direct gas chromatography (Berck, 1975).

5. In Biological Material

Acrylonitrile is not usually measured in biological material. Rather, the presence in the blood or urine of thiocyanate, a metabolite of acrylonitrile, is often used as an index of acrylonitrile exposure (e.g. Malette, 1943; Lawton et al., 1943; Efremov, 1976). The colorimetric methods described by Lawton et al. in 1943 are still used (e.g. Gut et al., 1975). For urine thiocyanate detection, urine is added to an albumin-tungstate reagent and sulfuric acid. Then a ferric nitrate reagent is added, and the absorbance is determined. Absorbance is determined again after the addition of mercuric nitrate. The difference in absorbance is compared to a reference curve for thiocyanate.

Kanai and Hashimoto (1965) determined the concentration of acrylonitrile in expired air, blood and urine by absorbance. They found that acrylonitrile in acid solution reacted with bromine in ultraviolet light and developed a pink color with benzidine-pyridine reagent; the absorbance of this color was then measured.

III. BIOLOGICAL EFFECTS

The biological effects of acrylonitrile in humans, animals, microorganisms and plants are discussed in the following sections. In animals, the metabolism and toxicity of acrylonitrile varies with duration of exposure, route of administration, and species (e.g. Gut et al., 1975; Young et al., 1977). Accordingly, sections on human and animal toxicology are subdivided first by duration of exposure then by route of administration and, where appropriate, by specific effect or species.

A. Humans

1. Acute Toxicity

Acute effects of acrylonitrile have been described for inhalation, dermal contact, and exposure to acrylonitrile-containing fumigants.

a. Inhalation Exposure

The effect of acute vapor inhalation has been described by Sartorelli (1966). A 22-year-old chemist was exposed to acrylonitrile vapors for at least two hours when a distillation apparatus leaked. Headache, vertigo, vomiting, tremors, uncoordinated movement and convulsions were observed. Vomiting and nausea persisted after 24 hours. Upon examination one day after exposure, the chemist showed slight enlargement of the liver and congestion of the oral pharynx, but no disorders of the central nervous system were noted; four days after exposure, no kidney, liver, cardiac or respiratory abnormalities were detected.

b. Dermal Exposure

An early case involved a male laboratory worker who spilled "small quantities" of liquid acrylonitrile on his hands (Dudley and Neal, 1942). After 24 hours there developed diffuse erythema on both hands and wrists. By the third day blisters appeared on the fingertips; the hands were slightly swollen, erythematous, itchy and painful. The fingers remained dry and scaly on the tenth day.

Schwartz (1945) reported acrylonitrile to be a "powerful skin irritant" that can cause dermatitis. Wilson et al. (1948) observed that direct skin contact causes irritation and erythema followed by scab formation and slow healing.

Acrylonitrile has been shown to be a sensitizer, promoting allergic contact dermatis (Balda, 1975). A 27-year-old individual developed dermatitis following the use of a "Plexidur" finger splint (copolymer of acrylonitrile and methyl methacrylate). A rash developed on the left middle finger where the splint had contacted the skin for over six weeks. Subsequent patch testing on this individual revealed a ++ positive reaction using both "Plexidur" and 0.1% acrylonitrile. Other acrylic resins and compounds are also implicated as dermal allergens (reviewed by Rycroft, 1977).

Acrylonitrile can penetrate clothing and leather shoes (American Cyanamid, 1976), thus contacting skin. For example, a chemical burn from acrylonitrile resulted after a worker failed to remove his shoes after "gross contamination of the shoes" (Dow Badische Co., 1977).

c. Fumigant Exposure

Home fumigation with acrylonitrile has resulted in both fatal and nonfatal intoxication of the returning occupants. In home fumigation, the usual practice is to place 3½ - pounds of AN-carbon tetrachloride or AN-methylene chloride mixtures per 1000 cubic feet in shallow open pans. Fans are used to circulate the vapors in a tented structure for 24-72 hours. The tent is removed and the operator decides when the house is safe for occupancy (Davis et al., 1973).

Home fumigation has been practiced in Florida. During 1971 in Dade County (Florida) alone there were 279 fumigations involving acrylonitrile. From January 1957 to October 1971, the Florida Bureau of Entomology reported a total of 24 acrylonitrile fumigation incidents; about equal numbers of carbon tetrachloride and methylene chloride mixtures were used. Some of these incidents involved more than one person, for a total of 8 fatalities and 41 nonfatal casualities (Davis et al., 1973).

Symptoms of nonfatal intoxications included lacrimation, burning in the throat, coughing, sneezing, dermatitis, nausea, vomiting, dizziness, visual disturbance, headache, coma and seizures (Davis et al., 1973).

Davis et al. (1973) described several fatal intoxications:

Case I. A 57-year-old alcoholic female was found dead after the tent used for fumigation was removed from her home; she apparently had not vacated the premises.

Case II. A 22-month-old male slept for one night in a room that had been fumigated 6½ hours previously; the child died four days later. Traces of cyanide were detected in the blood. The brain was swollen and softened; the pituitary was necrotic.

Case III. A 67-year-old man died within 24 hours of returning to his house that had been fumigated. The man had a past history of hypertension. Autopsy revealed heart disease, emphysema, liver congestion and cystic infarcts of the basal ganglia and pons. Trace amounts of cyanide were detected in the blood.

Case IV. A 41-year-old female returned 20 hours after her apartment had been fumigated, and died 24 hours later. At autopsy, focal pulmonary congestion and edema were found. Cyanide was found in several tissues.

Case V. A 63-year-old female died several days after fumigation, showing signs of tremors and respiratory failure.

Grunske (1949) described another fatal case. A three-year-old girl died the night after her parent's home was fumigated with acrylonitrile to control an insect infestation. A doctor attributed death to hydrocyanic acid poisoning, noting these signs: breathing disorder, unconsciousness, paleness, tachycardia. Grunske (1949) also briefly mentioned 3 additional deaths in children directly attributable to acrylonitrile fumigation. He cautioned that children may be particularly sensitive to acrylonitrile.

Radimer et al. (1974) described 1 nonfatal and 3 fatal cases of nonstaphyloccal toxic epidermal necrolysis (resembling second-degree burns) induced by a fumigant mixture (AN-CCl_4) used in Florida. Skin disease appeared 11 to 21 days after homes of the patients were fumigated.

Radimer et al. (1974) do not exclude the possibility that carbon tetrachloride may have been the responsible agent. CCl_4 acts as a CNS depressant in high doses and a liver toxin with delayed death at lower doses; however, such was not observed here. Moreover, as acrylonitrile is known to cause blisters when absorbed into workmen's shoes, they suspected acrylonitrile as the likely agent. The author's suggest inhalation of vapors as the likely route of exposure, rather than absorption through the skin.

The four cases are described below:

Case I. Three weeks after her house was fumigated, a 64-year-old woman developed a pruritic eruption on the abdomen and blisters on the feet. This condition progressed until more than 90% of the skin was covered with bright erythema and large bullae. The epidermis was necrotic and separated from the dermis. Despite supportive therapy, the woman died 2 days later.

Case II. One and one-half weeks after domicile fumigation the skin of a 41-year-old woman became erythematous. This condition worsened into a generalized bullous dermatitis, covering the body by day 21. The woman died on day 27.

Case III. Seventeen days after fumigation, the skin of a 36-year-old woman was erythematous and covered with vesicles and flaccid bullae. Preceding dermal symptoms were the following: sore throat, weakness, dizziness, vomiting, and burning sensation of the eyes. The woman died on day 26.

Case IV. The 10-year-old son of Case 2 developed pruritic eruptions that covered one third of his skin 2 weeks after fumigation. New eruptions emerged over the next few days, but treatment was successful in preventing death.

Lorz (1950) reported a fatal case of acrylonitrile (Ventox) poisoning resulting not from vapor inhalation, but rather, from direct skin application. A mother applied Ventox to the head of her 10-year-old girl to control head lice; the head was wrapped in a towel and the child was sent to bed. Before falling asleep, the child complained of feeling ill, dizzy and having a headache; she threw up several times. The girl became unconscious and went into convulsions and died the next day.

2. Occupational Exposure

The National Institute for Occupational Safety and Health estimates that 125,000 persons are potentially exposed to acrylonitrile in the workplace (Finklea, 1977). During 1977, NIOSH and OSHA (Occupational Safety and Health Administration) requested manufacturers and end-users of acrylonitrile to submit information on acrylonitrile, including employee exposure. Information received in response to these requests is summarized in Table 22 for the number of employees exposed and the processes in which these workers are exposed. The current OSHA standard for occupational exposure to acrylonitrile is an 8-hour time weighted average of 2 ppm. NIOSH recommended that acrylonitrile be handled in the workplace as if it were a human carcinogen and recommended industrial hygiene practices to reduce exposure be implemented (Finklea, 1977).

Measurements at a U.S.S.R. production site confirmed that acrylonitrile is not just an air contaminant, but is present on equipment and clothing as well (Zotova, 1975). Samples of workroom air (N = 452), washings from equipment (N = 82), washings from worker's skin (N = 398), and clothing patch samples (N = 35) were taken over a 5 year period (1965-1971). Initially the workroom air exceeded the Mean Permissible Concentration (MPC = 0.5 mg/m^3) by 5-10 times. However, this was reduced to an average of 0.75 mg/m^3 after sanitary measures were instituted.

Table 22

Processes in Which Workers are Exposed to AN at Representative Production Sites (as reported to OSHA)

Company	Processor Division	Number Exposed[a]
SOHIO	Barex resin manufacture	41
	AN manufacture	38
American Cyanamid	AN manufacture	209 overall
	Acrylamide manufacture	
	Truck and Barge loading	
	Laboratory and Plant Operations	
	Iminodipropionitrile manuf.	
	XT polymer production	
	Paper products production	
	Acrylic Staple & Tow	
	Cypcin production	
DuPont	Elastomer Chemicals Dept.	1,200 (since 1940)
	Organic Chemicals Dept.	450 (since 1953)
	Fabric & Finishes Dept.	350 (since 1955-1958)
	Textile Fibers Dept.	2,000 (since 1950)
	Polymer Intermediates Dept.	350 (in 1976)
	Elastic Products & Resins	30 (since 1955)
	Plastic Products & Resins	120 (since 1956)
	Waynesboro, Va.	1,800 (since 1945)
Texaco	Speciality Chemicals	51
B. F. Goodrich	Hycar rubber & ABS production	84
	AN manufacture	60-70 (1954-1972)
Borg-Warner	All processes	100 exposed for 20 years
Dow Chemical	AN/Styrene copolymerization	178
	AN/vinylidene chloride copolymerization	50
	Chemical Intermediates	35
Union Carbide	AN manufacture 1947-1977	50 in 1977
	AN manufacture 1954-1966	47
	Silane	70
	Others	277
Dow Badische	Polymerization & wet spinning	65
Uniroyal	ABS resin AN-butadiene rubber	344 (1976-1977)

[a] numbers refer to workers exposed during 1976-1977 except as noted

found to be contaminated with acrylonitrile were: equipment (0.002 mg/cm^2), handrails of stairways (0.0056 mg/cm^2), doors and door handles (0.0168 mg/cm^2), windows and floors.

By the end of a shift acrylonitrile was found to have accumulated on worker's skin (> 2 mg accumulated on the palms of apparatus operators, machinists and laboratory workers) and clothing (.00024-.00074 mg/cm^2 in one day). Acrylonitrile was not easily removed from the skin and clothing by ordinary washing; a protective paste of household soap, mineral oil, glycerine and china clay reduced AN content on the palms of hands by 67%.

a. Signs and Symptoms

Workmen exposed to "mild concentrations" of acrylonitrile in synthetic rubber manufacture developed nausea, vomiting, weakness, nasal irritation, and an "oppressive feeling" in the upper respiratory tract (Wilson, 1944). Sometimes symptoms of headache, fatigue and diarrhea were observed. In a few cases mild jaundice appeared, lasting for several days and was accompanied by occasional liver tenderness. One severe case of jaundice lasted for four weeks although the individual complained of "lassitude and fatigue" after one year. Cases of jaundice were accompanied by low grade anemia.

In 15 years, Zeller et al. (1969) treated a total of 16 workers who inhaled acrylonitrile fumes. Symptoms appearing within 5 to 15 minutes were nausea, vomiting, headache and vertigo. In no case was hospitalization necessary.

Workmen exposed to atmospheres containing 16-100 ppm acrylonitrile for 20 to 40 minutes during cleaning operations in polymerizers frequently complained of a dull headache, fullness in the chest, irritation of all mucous membranes (including eyes, nose, and throat), and a feeling of apprehension and nervous irritability (Wilson et al., 1948). Some workmen had "intolerable itching" of the skin but no accompanying dermatitis. Direct skin contact with acrylonitrile caused irritation and erythema.

Zeller et al. (1969) treated 50 cases (in 15 years) of skin damage resulting from occupational contact with acrylonitrile. Symptoms occurred 5 minutes to 24 hours after contact. Initially there is a burning sensation, followed by a reddening of the area, which often blisters after one day.

A group of Japanese workers employed in acrylonitrile manufacture complained of headache, weakness, fatigue, nausea, vomiting, nosebleed, and insomnia (Sakurai and Kusumoto, 1972). These symptoms correlated significantly with length but not with degree of exposure or age of the worker (Table 23). In all, 576 workers were examined several times so that a total of 4439 health records were available for analysis.

The health of Russian workers was assessed in 45 individuals employed in acrylonitrile manufacture from 4-6 years and compared with 25 control individuals (Zotova, 1975). Acrylonitrile workers complained of poor health, headache, decreased work capacity, poor sleep, irritability, chest pains, poor appetite and skin irritation (irritation during the first months of employment only). Paleness of the skin was noted in many workers.

Spassovski (1976) reported toxic and allergic dermatitis occurring among acrylonitrile workers in Bulgaria. According to Spassovski (1976) cumulative effects of acrylonitrile may not be detected due to the worker's short length of service (3-5 years). Anton'ev and Rogailin (1970) reported dermatitis among Russian acrylonitrile workers.

Table 23

Association Between Abnormal Findings and Several Variables Associated with AN Exposure (Sakurai and Kusumoto, 1972)

	Age[b]	Length of Exposure[c] Total	Group I	Degree of Exposure[d]	N
Subjective Complaints					
Heaviness in Head	no[a]	*yes/+[a]	yes/+	yes/+	4,439
Headache	no	*yes/+	yes/+	? /+[a]	4,439
Weakness	*yes/-[a]	*yes/+	yes/+	yes/+	4,439
Fatigue	? /-[a]	*yes/+	yes/+	? /+	4,439
Nausea	no	*yes/+	yes/+	yes/+	4,439
Vomiting	no	*yes/+	yes/+	yes/+	4,439
Nosebleed	no	*yes/+	yes/+	yes/+	4,439
Insomnia	no	*yes/+	yes/+	yes/+	4,439
Inspection					
Skin eruptions	no	no	no	no	4,439
Pallor	no	no	no	no	4,439
Jaundice	no	no	no	no	4,439
Conjunctivitis	no	no	no	no	4,439
Specific Gravity of Whole Blood	*yes/-	no	no	no	3,520
Serum Colloid Reaction					
Lugol-Test	?/+	yes/+	? /+	no	1,544
Hayem-Test	?/+	yes/+	yes/+	*yes/+	3,794
CCLF	no	no	no	no	4,293
Serum Cholinesterase Activity	no	*yes/+	? /+	no	3,247
Urine Tests					
Urobilinogen	*yes/-	*yes/+	*yes/+	*yes/+	4,313
Bilirubin	no	no	no	no	4,354
Protein	yes/+	? /+	no	yes/+	4,350
Glucose	? /+	no	no	no	3,511

[a] Scoring: no = no association; yes/+ = positive association: yes/- = negative association; ?/+ = probable positive association; ?/- = probable negative association

* significant at 95% level

[b] 15 to 49 years old

[c] employment 0->10 years

[d] data for both groups lumped together by authors (group I - working environment ~ <5 ppm AN group II- working environment ~ <20 ppm AN)

b. Hematological Alterations

Workers engaged in the production of acrylonitrile have exhibited hematological changes (Shustov, 1968). Compared to controls (a group of blood donors), some employees showed slightly lowered hemoglobin, leucocyte, erythrocyte and neutrophil counts; non-hemoglobin iron and the number of lymphocytes were increased (Table 24). Shustov (1968) observed inhibited maturation of normoblasts (late stage in red blood cell formation) and disturbed formation of bone marrow. It is suggested that the disturbed hemoglobin levels might be related to inhibited enzymatic activity while the reduction in leucocytes might be due to changes in the mitotic activity of the white marrow cells. Workers were exposed to levels of AN at 5-10 times the Mean Acceptable Concentration (0.5 mg/m^3).

Table 24

Some Indicators of Peripheral Blood in Donors
and Workers Involved in AN Production
(Shustov, 1968)

Group	Hemoglobin (g %)	Erythrocytes (millions)	Plasma Fe(µg%)	Leukocytes (thousands)	Neutrophils (%)	Lymphocytes (%)
Donors						
Male (100)	15.0 ± 0.2 (12.5-17.0)	4.8 ± 0.1 (4.0-5.5)	85 ± 12 (65-110)	6.6 ± 0.8 (4.2-9.2)	64 ± 10 (55-73)	26 ± 5 (21-30)
Female (100)	13.1 ± 0.2 (11.7-16.1)	4.3 ± 0.1 (3.8-5.0)	76 ± 0.6 (50-100)	7.2 ± 0.6 (4.4-9.5)	66 ± 10 (56-75)	27 ± 4 (23-30)
AN Workers						
Male (10)	14.0 (12.2-14.7)	3.9 (3.8-4.2)	110 (85-140)	4.0 (3.1-4.5)	50 (42-60)	41 (35-45)
Female (25)	12.5 ± 0.1 (11.3-14.0)	3.7 ± 0.1 (3.1-4.0)	115 ± 15 (80-150)	3.8 ± 0.7 (2.6-5.7)	55 ± 7 (48-67)	42 ± 5 (28-53)

Analysis of blood samples in Russian workers exposed to acrylonitrile revealed significantly lower erythrocyte counts in laboratory workers and female apparatus workers and lower leucocyte counts in female apparatus workers and machinists (Zotova, 1975; Table 25).* Hemoglobin was lowered in all apparatus operators and laboratory workers. Catalase activity was reduced for all categories of workers examined. Total glutathione was increased among male apparatus workers, machinists, and lab workers; all workers showed an increase in oxidized glutathione. Also, all workers had a reduced sulfhydryl count. Changes from controls for these parameters can be taken as a measure ot toxicity and would likely reduce worker' ability to withstand further toxicological insult. The full significance of these parameters is not considered by the authors

Some workmen at B. F. Goodrich Company during the 1940's were routinely exposed to "several atmospheric concentrations" of acrylonitrile for 20 to 45 minutes at a time. Blood thiocyanate levels in those individuals exposed to concentrations below 22 ppm for 30 minutes returned to normal after 2½ hours. However, elevated levels were still present 12 hours after exposure to more than 50 ppm for 30 minutes (Wilson & McCormick, 1949).

c. Effects on Tissues and Organs

Sakurai and Kusumoto (1972) reported health impairment and especially liver function abnormality among acrylonitrile workers in Japan. They examined health records of 576 workers at 5 plants. A total of 4,439 health records were evaluated; each person was examined an average of 7.7 times. (However, no control population was examined.) Degree of exposure was classified as 2 types: I, working environment approximately less than 5 ppm and II, working environment less than 20 ppm AN (presumably greater than 5 ppm). Exposure was further broken down by length of employment (0-4, 5-9, > 10 years) and by age of worker (15-19, 20-29, 30-39, 40-49). Parameters examined are listed in Table 23.

*see page 79 for exposure level

Table 25

Blood Values of Workers Engaged in the Production of Acrylonitrile in Russia (Zotova, 1975)

	Control		Apparatus Operators[a]		Machinists[a]	Laboratory Workers[a]
	F N=13	M N=12	F N=28	M N=10	N=10	N=27
Erythrocytes ($\times 10^6$)	4.16±0.449	4.48±0.066	3.93±0.053	4.54±0.098	4.29±0.094	* 3.92±0.063
Leucocytes ($\times 10^3$)	6.32±0.31	7.28±0.25	6.36±0.22	6.12±0.49	*5.90±0.32	5.96±0.18
	12.65±0.27	14.64±0.27	*10.90±0.14	13.40±0.52	*12.55±0.26	11.90±0.33
Hemoglobin (g%)	3.77±0.14	3.42±0.13	* 2.63±0.09	*2.79±0.17	3.21±0.13	* 3.36±0.08
Catalase Index	0.31±0.014	0.28±0.013	* 0.21±0.008	*0.22±0.014	*0.19±0.011	* 0.21±0.011
Total Glutathione (mg%)[b]	37.70±1.36	35.50±0.39	38.22±1.42	*39.38±2.29	*38.90±1.18	*35.70±0.90
Reduced Glutathione	32.51±1.17	29.75±0.51	24.75±0.72	*25.82±1.59	28.09±2.12	*23.81±0.84
Oxidized Glutathione	5.20±0.48	5.75±0.25	*13.47±1.09	*13.56±2.12	*9.81±1.34	*11.89±0.84
SH groups (mM/100 ml)	1236±24.2	1353±22.19	*1042.9±22.9	*1141±56	*1140±47.3	*1123.7±23.5

*p<.05

[a] particular functions of these job descriptions are undefined in original reference

[b] the significance of changes in glutathione and sulfhydryls are discussed in in section III-B-3-4)-d.)

Correlation of these parameters with age of worker, length of exposure and degree of exposure was determined by chi-square tests or by regression analyses. Subjective complaints have been discussed (Section III-A-2-a).

There was no association between skin eruptions, skin color, jaundice, conjunctivitis and age or any of the variables associated with acrylonitrile exposure. Positive nonsignificant associations were found for the Lugol reaction and Hayem flocculation tests (both serum colloid reaction tests) and total length of exposure. Significant positive associations existed between these variables: the Hayem test and degree of exposure; serum cholinesterase activity and total length of exposure; urine urobilinogen and length of exposure; urine urobilinogen and degree of exposure.

Sakurai and Kusumoto (1972) conclude that mild liver injury (in some individuals) is indicated by these results. As significant associations existed between length of employment and several parameters, the authors feel that workers suffer slight chronic, cumulative effects from acrylonitrile. However, they knew of no specific worker whose health was consistently lowered from one health examination to the next that could definitely be attributed to acrylonitrile. Since even workers exposed to low acrylonitrile levels (< 5 ppm) had subjective health complaints, the authors question the allowable limit of 20 ppm in Japan.

Agayeva (1970) reported central nervous system impairment resulting from chronic acrylonitrile exposure. A group of 122 Russian workers involved in acrylonitrile production were examined; the length of exposure is not specified. These workers were divided into 3 groups after data were collected. Of these 122 workers, 77 (Group I) showed significant decreases in an "epinephrine-like substance" and increased in acetylcholine, compared to 30 healthy individuals; cholinesterase activity was unchanged (Table 26). Of these 77 workers, 34% had lowered arterial blood pressure and 62% had the following: labile pulse, alteration of the Aschner test (slowing of pulse following pressure on eyeball), diffuse dermographia, and increased sweating.

A second group of 27 workers out of the total 122 examined had elevated epinephrine levels (Table 26). Almost half of the workers in this group showed the following signs: neurasthenic syndrome, instability of arterial pressure, tachycardia-like pulse rate, and change of orthostatic reflex.

A third group of 10 workers did not differ from the controls in the parameters examined. However, these 10 workers were re-examined a year later; 7 workers showed decreased blood levels of epinephrine and 5 showed increased acetylcholine (values not given). From these limited data Ageyeva (1970) concludes that an "increasing service record" is accompanied by lowered epinephrine and increased acetylcholine (Why Group II individuals did not fit this pattern is not explained.) Individuals from Groups I and II were not re-examined. According to the author, impairment of the central nervous system results from chronic acrylonitrile exposure. However, the author apparently divided the workers into 3 groups after results were obtained, severely limiting the usefulness of this study.

Several other Russian studies are available which include a discussion of the toxic effects of acrylonitrile in workers. However, workers were exposed to other substances in addition to acrylonitrile. For example, Ostrovskaya et al. (1976) reported electrocardiogram shifts in workers

Table 26

Changes in Some Blood Values in Workers
Chronically Exposed to Acrylonitrile
(Ageyeva, 1970)

	Concentration in the Blood		
	Epinephrine-like substance[a] (µg %)	Acetylcholine[b] (equiv. units)	Cholinesterase[c] (equiv. units)
Healthy individuals (N = 30)	4.4 ± 0.28	0.046 ± 0.004	0.36 ± 0.02
AN workers[d] (122 total):			
Grp. I (N = 77)	2.6 ± 0.08*	0.058 ± 0.002*	n.s.
Grp. II (N = 27)	8.5 ± 0.41*	n.s.	n.s.
Grp. III (N = 18)	n.s.	n.s	n.s.

*significantly different from control (p < .001)

n.s. - not significantly different from control (values not given in text)

[a] determined by method of Gosh, Dev and Banerjee

[b] determined by method of Khestrin

[c] determined by method of Augustinsson and Heimberger

[d] groups apparently divided after results obtained

exposed in the workroom to acrylonitrile, acetonitrile, hydrocyanic acid and higher than permissible levels of noise. Mavrina and Il'ina (1974) reported increases in immunologic reactivity among trade school students exposed to AN, sodium thiocyanate and methyl acrylate. Orushev and Popovski (1973) observed clinical and electrocardiogram anomalies among 20 workers exposed to AN (3.0-20.0 mg/m^3 in air) and other substances during fiber production. Shustov and Mavrina (1975) and Mavrina and Khromov (1974) reported changes in the liver and the nervous, cardiovascular and gastrointestinal systems among workers occupationally exposed to acrylonitrile, methylacrylate and sodium rhodanite during fiber production. Nervous system changes, mainly vegetative alterations, were particularly noted among the 340 workers examined. Skin changes were also observed: dryness, desquamation, hand fissures, and diffuse erythema characterizing dermatitis.

d. Possible Carcinogenic Effects

A preliminary report on an epidemiologic study being conducted by DuPont indicated excess cancer incidence and cancer mortality among workers exposed to acrylonitrile (O'Berg, 1977). This study focused on a cohort of 470 males exposed to acrylonitrile at DuPont's textile plant in Camden, South Carolina at some time during 1950 to 1955; these workers are still actively employed by DuPont or have retired. A more complete analysis is planned which will include persons who were exposed to acrylonitrile but no longer work for DuPont. Smoking histories were not available.

Eight cancer deaths occurred among the cohort of 470 workers between 1969 and 1975 (this allows for a 20 year latency). Only 4 such deaths would be expected based on DuPont's Mortality Rates (1969-1975). About 5 deaths would be expected based on national rates for U.S. white males (1970) or regional rates in South Carolina (1969-1971). In the exposed group, 4 of the 8 deaths were from lung cancer, the rest resulted from cancers occurring at different sites.

The number of cancer cases occurring between 1969-1975 was higher among actively employed workers: 16 cases compared to 5.8 expected, based on DuPont Company rates or 6.9 expected, based on national rates. Data for the cancer cases were from DuPont's Cancer Registry. These 16 cases included cancer of the lung (N = 6), large intestine (N = 3) and 7 other primary sites.

For the cohort of 470 workers, there were a total of 18 cases of cancer and/or cancer deaths (data from DuPont's Mortality File and/or Cancer Registry) between 1969-1975. Cancer occurred at these sites: lung (N = 6), large intestine (N = 3), prostate (N = 2), lymphosarcoma (N = 1), Hodgkins (N = 1), penis (N = 1), thyroid (N = 1), nasopharynx (N = 1), bladder (N = 1), pancreas (N = 1).

DuPont stresses the preliminary nature of these data. Further analyses and additional data gathering are in progress.

The DuPont study has raised serious concern about the safety of acrylonitrile. Other epidemiological studies are currently underway or are being planned. Preliminary tabulation of mortality among workers at Uniroyal's Baton Rouge/Scotts Bluff Plant (La.) where ABS resin is manufactured revealed 6 deaths from cancer out of 30 total deaths (Uniroyal, 1977). Five of the 6 workers who died of cancer had been employed 8-20 years ($\bar{x}$ = 13.8 years) in resin manufacture. Dow Chemical Company made a preliminary review of mortality in workers with acrylonitrile exposure which revealed "no pattern of increased mortality due to malignant neoplasms". One employee of Dow Badische Co. with "routine exposure to acrylonitrile" developed cancer of the liver and gallbladder. For over one year, this worker was exposed to 5-10 ppm TWA (time weighted average) as a dry plant operator. As a dry area worker, he was exposed to < 1 ppm for 2 years (Dow Badische Co.,

The following is a list of companies undertaking or planning epidemiology studies of workers exposed to acrylonitrile:

1. DuPont - further analysis of cancer deaths and cancer cases; see above
2. American Cyanamid (1977) - examining the feasibility of an epidemiological study
3. Uniroyal (1977) - expects to begin epidemiological studies, under the auspices of the University of North Carolina, at their Baton Rouge/Scotts Bluff plant (La.). An ABS terpolymer (Kralastic) is manufactured there
4. Dow Chemical (1977b) - 2 studies currently ongoing but not specific for acrylonitrile
5. Union Carbide (1977) - epidemiology studies underway for all employees at their Bound Brook (NJ) and Sistersville (VA) plants; these studies are not specific for acrylonitrile
6. Monsanto (1977b) - epidemiology study on-going at locations where acrylonitrile has been produced (Alvin, Texas; Texas City, Texas) or used (Decatur, Ala.; Addyson, Ohio) for 8-26 years.
7. Vistron (1978) - epidemiology study begun in 1977 covering monomer and polymer production (Lima, Ohio)

3. Controlled Studies

Liquid acrylonitrile was applied to the forearm skin of 4 human volunteers (Rogaczewska and Piotrowski, 1968). Based on losses from the skin surface, it was determined that the absorption rate of acrylonitrile averaged 0.6 mg/sq cm/hour.

The retention of doses of acrylonitrile in the respiratory tract averaged 46 ± 1.6% in 3 men exposed to about 20 μg/l for up to 4 hours (Rogaczewska and Piotrowski, 1968). Retention did not vary between length of exposure but did vary between individuals, as these data show:

Retention of Acrylonitrile (%)

	Minutes Exposed to 20 μg/l AN						
Individual	0-10	10-30	30-60	60-90	90-120	120-180	>180
1	59	63	41	52	45	41	55
2	46	44	45	47	45	50	48
3	49	23	29	54	48	32	49
$\bar{x}$	51	43	38	51	46	43	51

These authors showed that absorption by inhalation is about 100 x more efficient than through the skin.

B. Nonhuman Mammals

The absorption, tissue distribution, biotransformation and toxicity of acrylonitrile to nonhuman mammals are discussed in the following sections. This information is then used to assess the mechanism of toxic action.

1. Absorption and Tissue Distribution

Young et al. (1977) specifically looked at absorption and distribution by using radio-labeled acrylonitrile. Radioactivity was determined by liquid scintillation counting but small sample sizes somewhat limited the usefulness of the experiments.

Young et al. (1977) calculated the percentage of oral acrylonitrile doses absorbed by male Sprague-Dawley rats (Spartan substrain) given single oral doses of 0.1 mg ^{14}C-AN/kg (4 rats) or 10 mg ^{14}C-AN/kg (5 rats). After

72 hours, the percentage of the dose recovered was 82.37% and 104.04% at 0.1 and 10 mg/kg, respectively (Table 27). Although significant dose related differences existed for recovery in the urine and carcass, both doses had a 5% recovery in the feces. Thus, about 95% of the dose had been absorbed.

Recovery of inhaled acrylonitrile (5 or 100 ppm for 6 hours) was determined in 8 rats exposed in a "nose only" inhalation chamber. More of the dose was recovered in the urine at the higher dose (Table 27).

The distribution of radioactivity of selected tissues was determined in rats given single oral or intravenous doses of ^{14}C-acrylonitrile (Young et al., 1977). All tissues examined (e.g. lung, liver, kidney, stomach, intestines, skeletal muscle, blood, etc.) contained acrylonitrile or its metabolites. High levels were found in the red blood cells, skin and stomach, regardless of route or dose. Radioactivity of the stomach walls was particularly high, even after i.v. administration, and therefore was not due to unabsorbed acrylonitrile when given orally. Analysis of the stomach after i.v. administration showed the amount of radioactivity increased from 30.33 μgEq at 5 minutes to 68.64 at 24 hours. (This may, in part, explain the significant increase in stomach tumors observed in rats given AN in chronic experiments [section IV-D]). The amount of radioactivity in other parts of the body was decreasing with time due to excretion, so this increase in the stomach revealed a selective secretion process.

2. Biotransformation

Acrylonitrile is metabolized in laboratory animals to cyanide, which is subsequently converted to thiocyanate and then eliminated in urine (e.g. Dudley and Neal, 1942; Brieger et al., 1952). However, less than one-quarter of an administered acrylonitrile dose has been accounted for by

Table 27

Recovery of Radioactivity from Rats Given Acrylonitrile by A) Oral Doses or B) Inhalation Exposure
(Young et al., 1977)

A. Oral	% of Dose Recovered at 72 hr[a]		Significance
	0.1 mg/kg (N = 4)	10 mg/kg (N = 5)	
Urine	34.22	66.68	$p < .05$
Feces	5.36	5.22	n.s.
Expired Air[b]	4.91	4.32	n.s.
Carcass	24.24	16.04	$p < .05$
Skin	12.78	10.57	n.s.
Cage Wash	0.86	1.22	n.s
Total	82.37	104.04	$p < .05$

B. Inhalation	% of Dose Recovered at 220 hr[a]		Significance
	5 ppm (N = 4)	100 ppm (N = 4)	
Urine	68.50	82.17	$p < .05$
Feces	3.94	3.15	n.s.
$^{14}CO_2$	6.07	2.60	$p < .05$
Body	18.53	11.24	$p < .05$
Cage Wash	2.95	0.85	n.s.
Total	99.99	100.01	

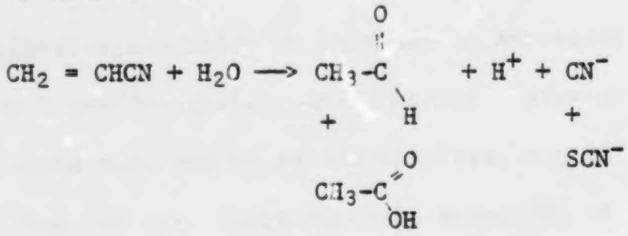
[a] standard deviation of values reported in original reference

[b] primarily as $^{14}CO_2$

this metabolic route (e.g. Benes and Cerná, 1959; Czajkowska, 1971; Gut et al., 1975). Acrylonitrile reacts with sulfhydryl groups (either cysteine or glutathione) by cyanoethylation, preventing further metabolism to cyanide and thiocyanate. Wright (1977) describes cyanoethylation as the preferred route. Other reactions may include coupling with D-glucuronic acid (Hoffman et al., 1976) and production of carbon dioxide (Young et al., 1977). Evidence from Gut et al. (1975), Young et al. (1977) and Wright (1977) shows the route, species and dose-dependent fate of acrylonitrile metabolism.

a. Biotransformation to Cyanide and Thiocyanate

A major metabolite of acrylonitrile is cyanide (CN^-), which is subsequently converted to thiocyanate SCN^-. The following mechanism has been suggested by Dahm (1977):



$$CH_2 = CHCN + H_2O \longrightarrow \underset{\displaystyle +\; CH_3\text{-}C(=O)OH}{CH_3\text{-}\overset{\displaystyle O}{\overset{\|}{C}}\text{-}H} + H^+ + \underset{\displaystyle +\; SCN^-}{CN^-}$$

Although earlier authors doubted that cyanide is a metabolic product of acrylonitrile (see discussion in Brieger et al., 1952), evidence now strongly favors this pathway. Evidence to this effect has been presented by Dahm (1977). Rats were fed radio-labeled acrylonitrile and five urinary metabolites containing labeling on the cyano group were later separated by high pressure liquid chromatography (HPLC). The peak suspected of being thiocyanate matched the retention times of thiocyanate standards. Also, thiocyanate was detected in the urine colorimetrically. A third experiment showed that when rats were fed acrylonitrile labeled on either of the 2 olefinic carbons, there was no thiocyanate peak by HPLC as there had been when the cyano group was labeled. Hence, the thiocyanate comes from the cyano carbon, as proposed above. Other authors have proposed the metabolic breakdown of acrylonitrile to thiocyanate via cyanide, using such evidence as: a) similarity of symptoms between cyanide and AN intoxication (Dudley and Neal, 1942); b) cyanide antidotes (e.g. sodium nitrile, sodium thiosulfate, hydroxycolbamine) offer some protection against acrylonitrile poisoning in some species (Dudley and Neal, 1942; Benes and Cerna, 1959; Graham, 1962); c) cyanide and cyanmethemoglobin have been directly measured in the blood after acrylonitrile administration (Brieger et al., 1952); d) thiocyanate has been directly measured in the urine after administration of acrylonitrile (Mallette, 1943; Lawton et al., 1943; Efremov, 1976).

Two studies are presented as examples of thiocyanate levels after acute acrylonitrile exposure. Lawton et al. (1943) exposed 3 to 6 female dogs to 0, 24, 40, or 60 ppm acrylonitrile vapor for four hours and measured thiocyanate levels up to 168 hours post-exposure. All but one treated dog showed peak serum thiocyanate levels within four hours of exposure. This level remained high for 8 to 24 hours and returned to near normal within 3 to 7 days. Urine thiocyanate increased 24 to 48 hours after exposure and decreased by days 4 to 6. There was no thiocyanate in the blood or urine of control dogs.

The evidence presented above shows only that cyanide and thiocyanate are metabolites of acrylonitrile. There has been some controversy over whether acrylonitrile's toxicity is due solely or partly to the cyanide or is unrelated to it (see Section III-B-4). Addressing this controversy, some investigators have determined the relative amounts of cyanide or thiocyanate formed after administration of acrylonitrile. For example, Benes and Cerná (1959) estimated only 19.4% of the acrylonitrile administered perorally to rats was metabolized to thiocyanate. Czajkowski (1971) determined 8.5% of acrylonitrile given i.v. to rats was metabolized to thiocyanate. Gut et al. (1975) emphasized that the amount of thiocyanate excreted in the urine varies between the route of administration and also between the species.

Gut et al. (1975) studied thiocyanate formation in female Wistar rats, albino mice and Chinese hamsters given 25.4 or 40 mg AN/kg by several routes (peroral, i.p., s.c., i.v.). In rats, there was a higher transformation after 48 hours of acrylonitrile to thiocyanate after oral (15-31%), than i.p. (2-6%) s.c. (6%) or i.v. (1%) administration. After oral dosing only, there was a distinct lag period before thiocyanate was detected suggesting that immediately after oral dosing, acrylonitrile is "not appreciably metabolized". Gut et al. (1975) also think that acrylonitrile is only slightly absorbed from the stomach. In mice there was also more thiocyanate excreted after oral (35% of AN dose) than i.p. (8-10%) or i.v. (11%) administration. In contrast to rats, more total thiocyanate was excreted. Gut et al. hypothesized a higher metabolic capacity and a possible lower binding capacity for acrylonitrile in mice. In addition, rates of transformation did not vary between i.p. and i.v. administration as they did in rats.

For hamsters, as in rats and mice, more thiocyanate was excreted in the urine after oral than after i.p. administration of acrylonitrile.

For both hamsters and mice there was no lag period before thiocyanate elimination after oral dosing, in contrast to a 4-hour lag in rats. Gut et al. (1975) suggest body size may be an influencing factor.

The authors also tested the effect of microsomal enzyme induction on the acrylonitrile-thiocyanate balance by pretreatment with phenobarbital. Similarly, the effect of microsomal enzyme inhibition was tested by pretreatment with SKF 525-A. In rats receiving either pretreatment followed by oral or intraperitoneal administration of acrylonitrile, thiocyanate metabolism was unchanged. Pretreatment of rats with cysteine or dimercaprol (both potential antidotes) also did not affect thiocyanate urine levels. However, pretreatment of rats or mice with thiosulfate significantly increased the metabolized portion of acrylonitrile when AN was given intraperitoneally (but not orally). The effect was most marked in mice; thiocyanate was increased more than 3 times over non-pretreatment levels. For rats, thiocyanate was increased almost twice.

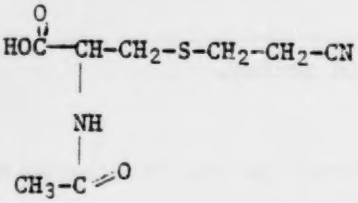
Gut et al. (1975) suggest that acrylonitrile-to-thiocyanate metabolism is "closely related to that portion of the dose of acrylonitrile reaching the liver during the first pass through the body after absorption". For acrylonitrile, distribution is probably closely related to strong binding and to non-enzymatic reactions. Gut et al. (1975) suggest strong binding in blood, and cyanoethylation reactions exclude acrylonitrile from further metabolism to thiocyanate. In summary, differences between route of administration (within a species) were caused by factors affecting the distribution of acrylonitrile, rather than by route-related metabolic differences. Gut et al. (1975) suggest cyanide-mediated toxicity is doubtful in rats but probable in mice.

b. Reaction with Sulfhydryl Groups

In addition to forming cyanide and thiocyanate, acrylonitrile reacts with sulfhydryl compounds by cyanoethylation. Hashimoto and Kanai (1965) showed that acrylonitrile forms stable conjugates with L-cysteine and L-glutathione *in vitro*. Thus, a portion of the acrylonitrile dose is prevented from being metabolized to cyanide and thiocyanate; this reaction is considered a detoxification mechanism. Gut et al. (1975) determined that acrylonitrile reacts with cysteine to form S-(2-cyanoethyl)cysteine, which is excreted in the urine.

Dahm (1977) unequivocally identified two conjugates of acrylonitrile with cysteine in rats given radiolabeled acrylonitrile:

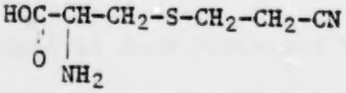
a)



$HO\overset{O}{\overset{\|}{C}}-\underset{\underset{\underset{CH_3-C=O}{|}}{NH}}{\underset{|}{CH}}-CH_2-S-CH_2-CH_2-CN$

(conjugation product of AN with cysteine and acetate)

b)



$HO\underset{O}{\underset{\|}{C}}-\underset{NH_2}{\underset{|}{CH}}-CH_2-S-CH_2-CH_2-CN$

(conjugation product of AN with cysteine)

Wright (1977), working out of the same laboratory as Dahm, administered orally cyano-labeled acrylonitrile to Spartan rats, a Charles River rat, and rhesus monkeys and measured metabolites collected for 24 hours in urine. As shown in Table 28, low levels of acrylonitrile (0.1 mg/kg) resulted in conversion of about 90% of the administered dose to N-acetylated cysteine and cysteine conjugate. At a higher dose (30 mg/kg) a greater proportion was excreted as thiocyanate and unidentified metabolite "C". Wright (1977)

Table 28

Urinary Metabolites Following the Oral Administration of C-1 (Cyano) Labeled Acrylonitrile
(Wright, 1977)

			Percent of Radioactivity in Urinary Metabolites*		
ANIMAL	N	DOSAGE (mg/kg)	cysteine-conjugates	"C" (unidentified)	thiocyanate
Spartan Rat	1	0.1	88.6	3.5	8.0
Spartan Rat	1	30.0	37.3	20.5	42.1
Charles River Rat	1	30.0	47.5	13.8	38.8
Rhesus Monkey	1	0.1	91.	6.	3.
Rhesus Monkey	1	30.0	84.	14.	2.

*0-20 hours in rats and 0-24 hours in monkey.

suggested that conjugation with cysteine is the "preferred metabolic excretory product", at dosages within the "normal metabolic capacity of the animal" (i.e., 0.1 mg/kg); only small amounts of acrylonitrile will be excreted in other forms. Wright further suggested that at higher doses (here, 30 mg/kg) this "preferred metabolic pathway" is overloaded, so other metabolic pathways are used.

As apparent in Table 28 there may be differences between the two strains of rats tested. However, the small sample sizes caution against a definite conclusion. These studies are continuing.

As evidence of an acrylonitrile-sulfhydryl reaction, depressed sulfhydryl levels resulting from acrylonitrile administration have been reported (e.g. Dinu and Klein, 1976; Hashimoto and Kanai, 1972; Vainio and

Mäkinen, 1977; Szabo et al., 1977). Details of these studies are discussed in Section III-B-3 of the Mammalian Toxicology section.

c. Coupling with D-Glucuronic Acid

Besides forming cyanide and thiocyanate or combining with sulfhydryl groups acrylonitrile can combine with D-glucuronic acid (Hoffman et al., 1976). Groups of 20 male Wistar rats were given 1/8, 1/4 or 1/2 the LD_{50} of acrylonitrile (82 mg/kg used as LD_{50}) by gavage. Rats given the 2 higher doses showed a significant increase in glucuronic acid excretion in the urine within 24 hours; levels of glucuronic acid returned to normal after 24 hours. Hoffman et al. (1976) suggested that acrylonitrile is initially hydrolyzed, after which the resulting product undergoes a condensation reaction with UDP-glucuronic acid.

d. Minor Metabolites

Young et al. (1977) identified CO_2 as a metabolite of acrylonitrile in rats. CO_2 was excreted in the breath and comprised 5 to 6% of the administered dose of acrylonitrile.

Dahm (1977) was unable to identify a metabolite of acrylonitrile ("metabolite C"), as it was unstable. He was unable to detect cyanide ion and free acrylonitrile in significant quantities in the urine. However, Hashimoto and Kanai (1965) and Hoffman et al. (1976) estimated that 15% of the administered dose of acrylonitrile is passed unchanged through the urine and breath.

Hashimoto and Kanai (1965) suggest acrylonitrile may be metabolized to acrylamide or acrylic acid. However, Young et al. (1977) do not think acrylamide is a possible metabolite.

e. Route and Dose Dependence of Metabolite Formation

Young et al. (1977) isolated 5 metabolites of acrylonitrile in rats. Except for carbon dioxide (excreted in the breath) these metabolites were not identified. Presumably, thiocyanate and cyanoethylation products were detected, but were not identified as such. Both a dose and route dependent fate were emphasized for all metabolites.

Male Sprague-Dawley rats (Spartan substrain) were given doses of 1-^{14}C-acrylonitrile by several routes. Samples of plasma, bile and urine were analyzed for metabolites by high pressure liquid chromatography. Five metabolites were resolved. Three of these (designated A, C, and E) comprised more than 95% of the total radioactivity and were excreted in the urine. A fourth metabolite, CO_2 was excreted in the breath. Metabolite A could not be distinguished from acrylonitrile by this method. Although urinary metabolites were not positively identified, the authors did determine that acrylamide was not a metabolite, as suspected by Hashimoto and Kanai (1965).

The proportion of the 3 metabolites in the urine was time dependent. The urine from one rat exposed to an atmosphere containing 5 ppm ^{14}C-AN for 6 hours was analyzed for metabolites after 0-8 hours and 40-48 hours. In the earlier sample the proportion of metabolites was: A, 18%; C, 70%; E, 13%. After 40 to 48 hours, however, the levels were quite different: A, 2%; C, 6%; E 92%.

The proportion of metabolites was also route and dose dependent (Table 29). Zero to 72 hour urine samples showed highest amounts of metabolite A (73%) after an oral dose of 0.1 mg/kg, but the maximum amount of metabolite B (61%) occurred after administration of 10.0 mg/kg. When

Table 29

Metabolites in Rats of ^{14}C-AN Separated by High Pressure Liquid Chromatography (Young et al., 1977)

Sample[a]	Percentage of Total ^{14}C[b] A	C	E
Urine, 0-72 hr.			
0.1 mg/kg; po	12	73	15
10.0 mg/kg; po	61	8	32
5 ppm, 6 hr.; inhalation[c]	9	30	61
100 ppm, 6 hr.; inhalation[d]	32	33	35
Bile, 1 hr.			
1 mg/kg; iv	2	91	1
Stomach, 24 hr.			
1 mg/kg; iv	4	3	93
RBC, 24 hr.			
1 mg/kg; iv	7	10	83
Plasma, 24 hr.			
1 mg/kg; iv	28	28	42

[a] sample sizes are not clearly stated for urine sample but are likely 4 or fewer per dose; for all other samples, data are from 1 rat

[b] total less than 100 when minor metabolites B and D were present

[c] equivalent dose 0.7 mg/kg

[d] equivalent dose 10.2 mg/kg

acrylonitrile was inhaled for 6 hours, a dose of 5 ppm resulted in 61% of metabolite E, while a dose of 100 ppm resulted in equal proportions of the 3 metabolites.

The metabolite pattern in the bile, stomach, red blood cells and plasma after intravenous administration is also summarized in Table 29. For the stomach RBC and plasma, E was the major metabolite at 24 hours (93, 83 and 42%, respectively). In the bile, metabolite C comprised 91% of the total radioactivity.

3. Toxicity

The effects of acrylonitrile administration to nonhuman mammals are discussed for acute, subacute and chronic exposures.

a. Acute Toxicity

1) Inhalation Exposure

a) Lethal Doses

Mortality data for acrylonitrile exposure to mice, rats, guinea pigs, rabbits, cats, dogs and monkeys are summarized in Tables 30, 31 and 32. Dogs appear most sensitive. One fatality occurred after 2 dogs were exposed to 140 mg/m^3 AN for 4 hours (Dudley and Neal, 1942) although all 6 dogs died when exposed to 217 mg/m^3 for 7 hours (Brieger et al., 1952). Fatalities occurred after 4 hours of exposure to 1250, 560 and 1300 mg/m^3 AN for guinea pigs, rabbits, and cats, respectively (Dudley and Neal, 1942).

Four fatalities occurred among 5 Osborne-Mendel rats exposed to 680 mg/m^3 for 4 hours (Dudley and Neal, 1942) but no deaths occurred in 6 Sherman rats exposed to 1085 mg/m^3 for 4 hours (Smyth and Carpenter, 1948). Only 1 death occurred among 6 mice exposed to 900 mg/m^3 for 1 hour;

Table 30

Inhalation Exposure to Acrylonitrile

Species/Strain	Sex/No.	Concentration converted units mg/m^3	Concentration original units conc.	Duration (hr)	Mortality	Reference
White Mouse/Stock[a]	NR/NR	5,800	5.8 mg/1	0.5	5/6	McOmie, 1949
		1,500	1.5 mg/1	0.5	5/6	McOmie, 1949
		600	0.6 mg/1	0.5	0/6	McOmie, 1949
		1,700	1.7 mg/1	1	6/6	McOmie, 1949
		900	0.9 mg/1	1	1/6	McOmie, 1949
		900	0.9 mg/1	2	3/6	McOmie, 1949
Albino Rat/Sherman[b]	F/6	1,085	500 ppm	4	2/6 or 3/6 or 4/6[c]	Carpenter et al., 1949
Rat/Sherman	NR/6	1,085	500 ppm	4	0/6	Smyth and Carpenter, 1948
		2,170	1,000 ppm	4	6/6	Smyth and Carpenter, 1948
Rat/Sprague-Dawley or stock	NR/12		saturated air	.05[e]	0/6	Zeller et al., 1969
Rat/Wistar	NR/NR	54.25	25 ppm	7	0/20	Brieger et al., 1952
		108.5	50 ppm	7	0/20	
		162.8	75 ppm	7	0/20	
		217.0	100 ppm	7	4/20	
Dog	NR/NR	108.5	50 ppm	7	0/4	Brieger et al., 1952
		162.8	75 ppm	7	0/ 4	
		217.0	100 ppm	7	6/6	
Rhesus Monkey	NR/NR	162.8	75 ppm	7	1/3	Brieger et al., 1952

NR = not reported

[a] 10 day observation; weight n.r.

[b] weight usually within 100-150 g

[c] unspecified; mortality within 14 days

[d] average weight 295 g

[e] shortest exposure time for mortality to occur (observed for 7 days)

Table 31

Inhalation Exposure of Acrylonitrile for 4 Hours in Various Mammal Species (Dudley and Neal, 1942)

Concentration	Mortality		
(mg/m^3)[a]	During Exposure	Total	Effects
		Guinea Pigs[b]	
210	0/16	0/16	slight to no effect
580	0/8	0/8	slight, transitory
1,250	2/8	5/8	eyes and nose irritated during test; delayed deaths (3-6 da) perhaps from lung edema
2,520	1/8	8/8	5 deaths 1.5 hr after test; 2 deaths after 18 hr
		Rabbits[c]	
210	0/3	0/3	slight; transitory
290	0/2	0/2	marked; transitory
560	1/2	2/2	death in 4-5 hr
1,260	1/2	2/2	death in 3-4 hr
		Cats[d]	
210	0/4	0/4	slight; transitory; salivation
600	0/2	0/2	marked; salivation; pain; no effects in 24 hr
1,300	0/2	2/2	convulsions; deaths 1.5 hr after test
		Dogs[e]	
63	0/3	0/3	slight salivation
140	0/2	1/2	survivor had severe salivation and was weak at end of exposure and died within 8 hr
213	0/3	0/3	2 had convulsions in 2.5 hr and coma at end of test (1 recovered in 48 hr; other had hind leg paralysis for 3 da); 1 had severe salivation and recovered in 24 hr
240	0/3	2/3	coma at end of exposure; deaths in 3-4 da; survivor refused food for 10 da

Table 31 (cont'd)

Inhalation Exposure of Acrylonitrile for 4 Hours in Various Mammal Species (Dudley and Neal, 1942)

	Rhesus Monkeys[f]		
140	0/4	0/4	slight initial stimulation of respiration
198	0/2	0/2	slight weakness during test; redness of face, genitals, etc.; normal in 12 hr

[a] original units mg/l, $mg/m^3 = mg/l \times 10^3$
[b] average wt 695 g; sex and age not reported
[c] albino; average wt 4530 g; sex and age not reported
[d] average wt 3620 g; sex and age not reported
[e] total 12 females, 1 male; average weight 8.1 kg (1 S.D.=2.6) ; age not reported
[f] total 4 females, 2 males; average weight 4.4 kg (1 S.D.=0.24); age not reported

Table 32

Inhalation Exposure of Rats[a] to Acrylonitrile (Dudley and Neal, 1942[b])

Duration of Exposure (hr)	Concentration (mg/m^3)[c]	No. Dying out of 16		Effects
		During Exposure	Total	
0.5	1,440	0	0	moderate transitory
	2,750	0	0	marked; no effects in 24 hr
	3,230	0	0	marked; no effects in 24 hr
	5,300	0	0	marked; slight residual effects in 24 hr
1.0	1,440	0	0	marked; transitory
	2,750	0	0	marked; normal in 48 hr
	3,230	0	4	death in 4 hr; slight residual effects at 24 hr
	5,300	0	13	Ibid
2.0	660	0	0	slight; transitory
	1,290	0	6	marked; transitory
	2,730	0	16	death in 4 hr
4.0	280	0	0	slight transitory
	680	4	5	marked; no effects in 24 hr
	1,380	8	16	death in 4 hr
8.0	200	0	0	slight discomfort
	290	0	0	moderate; transitory
	460	1	1	marked; transitory
	590	7	7	marked; no effects in 24 hr
	690	15	15	fatal

[a] adult Osborne-Mendel strain; average weight 295 g; sex not reported

[b] exposure was in an animal chamber with an input of air saturated with AN; a fan in the chamber mixed the air; Mg AN/l air was calculated from the amount of AN introduced and the total volume of air passing through the chamber.

[c] original units in mg/l.

3 deaths occurred after 2 hours exposure at 900 mg/m^3 (McOmie, 1949).

Jaeger et al. (1974) reported a 4 hour LC_{50} of 275 ppm (597 mg/m^3 for fasted rats. This concentration was without apparent effect on fed rats.

Knobloch et al. (1971) reported LC_{50} (4 hour) values of 300 mg/m^3 for mice, 470 mg/m^2 for rats and 990 mg/m^3 for guinea pigs.

In most cases death did not occur during the 4-hour exposure period but rather 1.5 to 18 hours thereafter. However, for longer exposures at higher concentrations, some deaths did occur during the exposure period (Tables 31 and 32; Dudley and Neal, 1942).

b) Signs

There are apparent dose and duration-related effects of acrylonitrile exposure, as well as species differences. In general, signs displayed in all species except guinea pigs given a lethal dose of acrylonitrile are: initial stimulation of breathing, followed by shallow rapid breathing, then slow gasping breathing; convulsions; coma, and death (Dudley and Neal, 1942). Effects are summarized in Tables 31 and 32.

Additional signs in several species are discussed below:

Mice. Toxic signs of acrylonitrile inhalation were described for Stock White mice exposed to 900-5800 mg AN/m^3 for 0.5 to 1.5 hours. Initially, activity increased and hyperpnea developed. Cessation of treatment at this point resulted in recovery without apparent after effects. If treatment continued, shallow breathing ensued, followed by gasping, apnea, and death. No gross changes were observed upon autopsy (McOmie, 1949).

Rats. The effects of acrylonitrile exposure in rats at several concentrations for up to 8 hours are summarized in Table 32. Concentrations of 5300 mg AN/m^3 for 0.5 hours were tolerated without residual effects while 690 mg/m^3 for 8 hours was fatal to all rats. Animals exposed to concentrations above 650 mg/m^3 showed mucus membrane irritation. The skin, nose, ears, and feet became flushed or reddened in all rats at all concentrations. This condition persisted for several hours after exposure. At the highest exposures there was a nasal exudate and watering of the eyes (Dudley and Neal, 1942).

Guinea Pigs. Guinea pigs tolerated up to 580 mg AN/m^3 for 4 hours without lasting effects (Dudley and Neal, 1942). At higher concentrations, the following signs were observed: watering of the eyes, discharge of nasal exudate, and coughing. Absent was the marked respiratory impairment observed in other species. Dudley and Neal (1942) suggested that acrylonitrile irritates the mucus and lung membranes in guinea pigs. There were some delayed deaths from lung edema.

Rabbits. Rabbits exhibited skin redness upon exposure to acrylonitrile but this was not as marked as in rats (Dudley and Neal, 1942).

Cats. Cats exposed to acrylonitrile showed skin redness, especially of the mucosa, salivation and vomiting; rubbing of the head and stomach was also observed (Dudley and Neal, 1942).

Dogs. Dogs exposed to 100 or 75 ppm (217 or 163 mg/m^3) for 7 hours vomited, and exhibited incoordination, convulsions and respiratory paralysis, although symptoms were milder at 163 mg/m^3 (Brieger et al., 1952). A slightly higher concentration (210 mg/m^3) for 4 hours produced convulsions as well as transitory paralysis in the hind quarters of one dog. Effects in these animals lasted 3-10 days, perhaps as a result of tissue anoxemia (Dudley and Neal, 1942).

Rhesus Monkeys. Two monkeys exposed for four hours to 198 mg/m^3 exhibited a slight reddening of the face, genitals and oral mucosa; there was some weakness and sleepiness (Dudley and Neal, 1942). Monkeys exposed to 163 mg/m^3 for 7 hours showed vomiting, respiratory distress, paralytic dilation of the pupil, cyanosis, then unconsciousness (Brieger et al., 1952).

2) Dermal Exposure

a) Lethal Dose Values

Lethal doses range from 250 to 840 mg/kg when acrylonitrile is applied directly to the skin of guinea pigs or rabbits (Table 33). Roudabush et al. (1965) determined the LD$_{50}$ of acrylonitrile to guinea pigs with abraded skin to be twice that of guinea pigs with intact skin.

Table 33

Acute Dermal LD$_{50}$ For AN

Species/Strain	Sex/No.	LD$_{50}$ (ml/kg)	Reference
Guinea Pig/Hartley derived	M/at least 12	0.46 intact skin[a] 0.84 abraded skin[a]	Roudabush et al., 1965
Guinea Pig	NR/NR	0.25[b]	Smyth and Carpenter, 1948
White Rabbit	M & F/at least 12	0.28 abraded skin[c]	Roudabush et al., 1965

NR = not reported

[a] Abdominal hair was removed in all animals by clipping and subsequently applying barium sulfide for a few minutes. In abraded skin tests, abrasions were made every 2-3 cm to penetrate the stratum corneum. AN applied on 1 sq inch cellulose pad. LD$_{50}$ calculated by method of Finney

[b] Range finding; determined by poultices.

[c] Hair was removed by clipping. Procedure described in Federal Hazardous Substances Labeling Act (21 CFR 191) except that skin was abraded (as described in footnote "a"). LD$_{50}$ calculated by method of Finney.

The dermal LD_{50} for Acrylon (AN and CCl_4) was 1.592 ml/kg in rabbits when applied directly on clipped skin and held in place with rubber sheeting (Tullar, 1947).

Although LD_{50} values were not calculated, Rogaczewska (1975) described concentrations of acrylonitrile that were fatal to rabbits. Acrylonitrile was not applied directly to the skin. Rather, intact rabbit skin (about 350 cm^2) was exposed to acrylonitrile vapors in an exposure chamber, with simultaneous isolation of the respiratory tract. Exposures of 620-440 mg/m^3 for 2.5 to 4 hours were fatal to the 3 rabbits tested. However, three rabbits exposed to 10-42 mg/m^3 for 2.5 to 4 hours survived. By exposing the respiratory tract while the skin was isolated, then comparing the concentration necessary to produce the same signs, Rogaczewska (1975) found that absorption rates through the skin and respiratory tract were quite different. At about the same length of exposure, fatalities from skin-only exposure occurred at about 100 times the acrylonitrile concentration found to be lethal when only the respiratory tract was exposed.

b) Signs

Direct application of acrylonitrile to the skin of rabbits produced edema and erythema at the application site (refer to the following section). In some cases, however, there may be distant reactions besides the local one.

Tullar (1947) placed a cuff of rubber sheeting around the body of rabbits, making contact with clipped skin. Two to 3 cc's of acrylonitrile (N = 2 rabbits) or 1-6 ml's of Acrylon (N = 15 rabbits) were pipetted into the cuff. Immediate reactions included struggling or pronation, difficulty in breathing, mild lacrimation, salivation and nasal discharge. Both acrylonitrile-treated rabbits died although the time to death was not stated.

If rabbit skin (315-350 cm^2) is exposed to acrylonitrile (440-620 mg/m^3 for up to 4 hours) in the air, rather than by direct application, slowing of the respiratory rate, convulsions and death occur (Rogaczewska, 1975).

c) Effects on the Skin

McOmie (1949) exposed the skin of three rabbits (sex not reported) to acrylonitrile at 1.0, 2.0, or 3.0 ml/kg. Rabbits' abdomens were shaved one day before treatment and acrylonitrile was applied directly; animals were prevented from inhaling the compound. The following data were obtained:

ml/kg	Area covered (cm^2)	Effect
1.0	100	slight local vasodilation; no systemic effects
2.0	200	slight local erythema; no systemic effects
3.0	200	slight local erythema; respiratory rate increased

Latency to toxic effects was not reported.

Tullar (1947) observed erythema only after application to abraded skin. Gauze pads containing 1.0 ml of acrylonitrile or Acrylon were applied to abraded and unabraded skin in 6 rabbits; rubber sheeting placed over the pads prevented evaporation. After 24 hours, mild erythema was observed in one of the 3 abraded areas to which acrylonitrile had been applied and

2 of 3 abraded areas to which Acrylon had been applied.

Zeller et al. (1969) determined the effect of acrylonitrile on the skin of white rabbits. The fur on the back was shaved. Acrylonitrile was applied to the skin on a cotton pad (2.5 x 2.5 cm) for 15 minutes or 20 hours. The reaction was graded from 0 (no effect) to 6 (necrosis). Over eight days, the 15 minute test was graded "3" (edema) and the 20 hour test was graded "6" (slight necrosis).

d) Effects on the Eye

McOmie (1949) instilled one drop of acrylonitrile (~ 0.05 ml) into the eye of a rabbit (sex not stated). There was immediate closure of the eye and shaking of the head. After 1 hour there was mild conjunctivitis without corneal clouding or pupillary damage, but after 24 hours no effects were observed.

One drop of acrylonitrile (~ 50 mm^3 or 0.05 ml) was placed on the eye of rabbits by Zeller et al. (1969) and after 8 days, edema and slight necrosis developed.

3) Oral Administration

a) Lethal Dose Values

The acute oral LD_{50} for acrylonitrile ranges from 25-128 mg/kg for laboratory mammals (Table 34). Mice appear most sensitive; LD_{50} values for several strains are between 25-48 mg/kg. Tullar (1947) reported male mice to be slightly more sensitive than females (36 *vs.* 48 mg/kg). Guinea pigs may be more tolerant than mice, as LD_{50} values range from 56-85 mg/kg. Rats are least sensitive to oral doses, the LD_{50} range being between 72-186 mg/kg.

Table 34

Acute Oral LD_{50} Values for AN

Species/Strain	Sex/No	Vehicle	LD_{50} (mg/kg)	Reference
White Mouse/Stock	-/4	-	$20 < LD_{50} < 72$	McOmie, 1949
Mouse	M/total M&F 333	water	36^a	Tullar, 1947
	F/-	water	48^a	Tullar, 1947
Mouse	-/169	olive oil	40^a	Tullar, 1947
Mouse/H strain	-/-	physiological solution	27^b 25^c	Benes and Cerna, 1959
Rat/Sherman	-/groups of 6-10	-	93^d	Smyth and Carpenter, 1948
Rat/Wistar	-	-	101^e	Paulet and Vidal, 1975
Rat/Wistar or Stock	-	-	128^f	Zeller et al., 1969
Rat/Wistar-Stamm	M/-	-	82^g (C.L.: 71.9-93.5)	von K. Borchardt et al., 1970
Rat/Wistar-Stamm	F/-	-	86^g (C.L.: 73.4-90.7)	von K. Borchardt et al., 1970
Rat	-/80	water	84^a	Tullar, 1947
Rat	-/51	olive oil	72^a	Tullar, 1947
Rat/Wistar	-	physiological solution	78^b	Benes and Cerna, 1959
Rat/Sprague-Dawley	M/20	1.0% aq. soln.	186^h (175-198)	Monsanto, 1975
Rat/Sprague-Dawley	F/20	1.0% aq. soln.	186^h (175-198)	Monsanto, 1975

Table 34 (cont'd)

Acute Oral LD_{50} Values

Species/Strain	Sex/No.	Vehicle	LD_{50}	Reference
Rat	-/-	-	62	Knobloch et al., 1977
Guinea Pig	/29	olive oil	85[a]	Tullar, 1947
Guinea Pig	M&F/30	-	56.94[i]	Jedlicka et al., 1957
Guinea Pig	M&F/30	-	56[j]	Jedlicka et al., 1957

[a] based on "accumulated" percentage mortalities; animals dying at a lower dose presumed susceptible to higher doses; LD_{50} computed graphically by plotting accumulated mortality against dose.

[b] technical grade (98% pure)

[c] chemical grade

[d] range finding

[e] method of Miller and Tainter; observed for 1 week

[f] observed for 7 days

[g] method of Litchfield and Wilcoxin

[h] method of Weil; 95% C.L.

[i] method of Behrens

[j] method of Trevan

Tullar determined LD_{50} values for acrylon which is used as a fumigant. Lethal dose values for mice, rats, and guinea pigs, calculated as mg/kg of acrylonitrile, were within the ranges reported above: mouse, 40 mg/kg; rat, 78 mg/kg; guinea pig, 75 mg/kg.

Acrylonitrile and potassium cyanide were administered jointly and the potentiation of acute toxicity was determined (Monsanto, 1975). Observed LD_{50} values of 3 mixtures of AN:KCN (1:1, 1:3, 3:1) were larger than the "expected" values based on known LD_{50} values of AN and KCN alone, thus showing there was joint action. However, Smyth et al. (1969) found fairly good agreement between predicted and observed LD_{50} values when testing the joint toxic action of acrylonitrile and each of 26 chemicals using the formula of Finney (1952):

$$^{1}/\text{predicted } LD_{50} = {}^{P}a/LD_{50} \text{ component A} + {}^{P}b/LD_{50} \text{ component B}$$

[P_a and P_b are the proportions of A and B in the mixture]

This formula is useful to assess the toxicity of a mixture of AN and another substance when their joint action is unknown.

b) Signs

Signs of acrylonitrile intoxication vary less between route of administration than between species and dose.

Mice. Mice (strain H) given lethal oral doses of acrylonitrile showed excitation within 5 to 10 minutes; movement became uncoordinated and then drowsiness occurred. Paresis of the limbs, tachypnea, cyanosis, and convulsions preceded death, which was due to asphyxiation and which occurred 20 to 120 minutes after dosing (Benes and Cerna, 1959).

Rats. Signs of acute acrylonitrile intoxication after oral administration in Sprague-Dawley rats included reduced appetite and activity, increasing weakness, tremors, collapse and death within 6 to 20 hours (Monsanto, 1975).

Benes and Cerna (1959) compared effects in mice and Wistar rats. Whereas mice show signs similar to that in cyanide poisoning (i.e., cyanosis), rats do not exhibit such respiratory distress. Rats fatally dosed with acrylonitrile show mild ruffling of the fur after 15 to 25 minutes, defecation, mild drowsiness, redness of the mucus membranes, ears and feet, vomiting and salivation. Convulsions appear within 3 to 4 hours followed by death after 3 to 5 hours.

Guinea Pigs. Fifteen guinea pigs (400 g) given 50 to 100 mg AN/kg orally showed lacrymal and nasal secretions and coughing within thirty minutes (Jedlicka et al., 1958). After sixty minutes there developed rapid, shallow breathing (without coughing), which gradually changed to abdominal breathing followed by tonicoclonic seizures and abdominal spasms; most animals showed hind limb incoordination. A short period of coma preceded death.

c) Tissue and Organ Changes

Guinea pigs (400 g) fatally dosed with 50 to 100 mg/kg showed lung edema, dilation of the right ventricle, filling of the coronary blood vessels, hepatic and splenic hyperemia, degeneration of the kidneys, hardening of the lymphatics of the stomach and intestines, and inflamed intestinal mucosa (Jedlicka et al., 1958). Similarly, Sprague-Dawley rats fatally dosed with acrylonitrile showed hemorrhagic areas of lungs and liver, and acute gastrointestinal inflammation (Monsanto, 1975).

Single oral doses of 10, 15, or 20 mg acrylonitrile resulted in adrenal hemorrhages in 10-40% of treated female ARS-Sprague-Dawley rats (Szabo and Selye, 1971).

4) Parenteral Administration

a) Lethal Dose Values

LD_{50} values for percutaneous administration of AN to mice, rats, guinea pigs and rabbits range from 15 to 130 mg/kg and average about 60 mg/kg (Table 35). In general, mice are least tolerant and guinea pigs most tolerant to acrylonitrile. Most data are available for mice; there appear to be slight differences between strains, sex, and route of administration. Wistar rats are less tolerant of subcutaneous injection than intravenous injection (Table 35; Knobloch et al., 1971).

b) Signs

Paulet et al. (1966) described symptoms of intoxication for rabbits given a lethal dose of 120 mg/kg acrylonitrile intravenously, but emphasized that signs vary little between species.

Four phases were seen:

i. Immediate Excitatory Phase, lasting 3 to 10 minutes. The animal is agitated, rubs the nose and cries.

ii. Quiet Phase, appearing after 15 to 60 minutes. The animal is immobilized, appears somnolent, after which slight trembling appears in the hind legs and later in the entire body (especially the head).

iii. Phase of Convulsive Epileptiform Crisis. Short bursts of tonic-tetanic convulsions (30-90 seconds each) appear during this phase, accom-

Table 35

Acute Parenteral LD_{50} Values for AN

Species/Strain, Sex	Route	Vehicle	LD_{50} (mg/kg)	Reference
White Mouse/NR	i.p.	NR	~ 15^{a}	McOmie, 1949
Mouse/ICR, F	i.p.	NR	46.99^{b}	Yoshikawa, 1968
Mouse/NMRI or SPF	i.p.	NR	50^{c}	Zeller et al., 1969
Mouse/NR, M.	i.p.	water	40^{d}	Tullar, 1947
Mouse/NR, F	i.p.	water	48^{d}	Tullar, 1947
White Mouse/NR	s.c.	0.9% saline	50 at 2 hr 25 at 24 hr	Graham, 1965
Mouse/H	s.c.	NR	35^{e}	Benes and Cerna, 1959
Mouse/BN	s.c.	NR	34^{f}	Knobloch et al., 1971
Rat/Wistar	i.p.	NR	100^{f}	Knobloch et al., 1971
Rat/Wistar	i.p.	polyethylene glycol	65^{g}	Paulet and Vidal, 1975
Rat/Wistar	s.c.	NR	80^{f}	Knobloch et al., 1971
Albino Rat/NR, M.	s.c.	NR	95.8^{h}	Magos, 1962
Guinea Pig/NR	s.c.	NR	130^{i}	Ghiringhelli, 1954
Guinea Pig/NR	i.v.	water	72^{d,j}	Tullar, 1947
Rabbit/NR	i.v.	NR	72	Paulet and Vidal, 1975

NR = not reported

[a] based on 2 stock mice

[b] adult female mice; based on method of van der Waerden

[c] observed for 7 days

[d] total males and females: 325; based on "accumulated" percentage mortalities, animals dying at a lower dose presumed susceptible to higher doses; LD_{50} computed graphically by plotting accumulated mortality against dose

[e] technical grade AN (98% pure); confidence interval 32.1-38.1; calculated by method of Litchfield and Wilcoxin

[f] method of Litchfield and Wilcoxin

[g] method of Miller and Tainter; observed for 1 week

[h] median lethal dose; determined by method of Dreichmann and LeBlanc

[i] 3-6 mo. old guinea pigs; weight 460 g

[j] 11 guinea pigs.

panied by loss of sphincter control. Each burst leaves the animal prostrate and exhausted, with gradual improvement between bursts.

iv. Paralytic or Terminal Phase. The hind limbs become immobile, convulsive crises become more frequent and body temperature drops. Paralysis progresses until death.

Paulet et al. (1966) stress that polypnea (increased respiratory rate) does not occur; this condition is characteristic of cyanide poisoning.

Descriptions by other authors, although less detailed, essentially agree with those of Paulet et al. (1966). For example, Ghiringhelli (1954) observed the following effects within 4 to 6 hours in guinea pigs (3-6 months old; 460 g) lethally dosed with 130 mg AN/kg subcutaneously: agitation, ruffling of the hair, tachypnea, tremors, diarrhea, vomiting, paresis, respiratory disturbances, cyanosis, and eventual death. In anesthetized dogs given intravenous injections of 1 to 100 mg AN/kg Graham (1965) observed: jactitation, convulsion, vomiting, defecation, irregular breathing, and sometimes apnea. Injection of 200 mg/kg resulted in continuing apnea and cardiac failure.

Symptoms of trembling and convulsions after acrylonitrile injection indicate central nervous system damage to areas of the midbrain (Paulet et al., 1966).

c) Effect on the Adrenals

Single doses of acrylonitrile (i.p. or p.o.) to female ARS/Sprague-Dawley rats (100 g) produced rapid bilateral adrenal apoplexy and necrosis (Szabo and Selye, 1971; Szabo et al., 1976).

Peroral doses of 10, 15 or 20 mg AN resulted in adrenal hemorrhages in 1, 2, and 4 rats, respectively, per group of 10 rats while 15 mg AN i.v. resulted in all 10 rats showing adrenal hemorrhages. Although the incidence was higher after i.v. injection, mortality rates for administration of 15 mg p.o and i.v. were not different.

Both groups (p.o. & i.v.) showed extensive hemorrhage in the adrenal cortex and, sometimes, the medulla and necrosis in the inner cortical zones; lesions were more pronounced on the right side.

Twenty mg of injected (i.v.) AN caused bilateral apoplexy to develop after 1-2 hours. Within 30 minutes, discontinuities developed in the endothelial lining of the adrenocortical capillaries. Later, extravasion of erythrocytes with loss of plasma fluid was observed, which eventually became massive. Parenchymal cells in the zona fasciculata appeared compressed and/or contracted.

A decrease in the number of blood platelets also occurred. Outward signs were cyanosis, excitement, tremor, and convulsions. With i.v. injection, head, neck, and often pulmonary edema were also observed.

To further describe adrenal apoplexy, Handin and Szabo (1977, meeting abstract) administered AN i.v. to 200 g female Charles River rats at 15 mg/100 g in 0.5 ml water; controls received water only. After 30 minutes blood samples revealed a significant increase in plasma fibrinogen. After 60 minutes there were the following statistically significant changes: thrombocytopenia, prolonged prothrombin time, partial thromboplastin time and thrombin time. Deposition of fibrin, which often obstructed blood vessels, was observed in the cortical sinusoids, adrenal medullary veins and, less frequently vessels of the lung. Handin and Szabo (1977) suggest these changes in blood coagulability and fibrin deposition might have a role in acrylonitrile induced adrenal apoplexy.

d) Effect on Sulfhydryls

Wisniewska-Knypl et al. (1970) suggested involvement of sulfhydryl groups to explain the mechanism of acrylonitrile toxicity upon the adrenal gland. Rats were injected subcutaneously with 100 or 200 mg/kg 3.5 or 1.5 hours, respectively, before killing. Respiration of tissue slices and activity of SH-enzymes were determined by standard methods.

At 200 mg/kg (but not 100 mg/kg) there was a significant decrease of oxygen uptake (after 30, 60, 90 and 120 minutes) in kidney cortex slices compared to controls. Doses of 100 or 200 mg/kg significantly reduced the activity of oxoglutarate dehydrogenase (but not succinate oxidase) in the liver and kidney and also reduced the level of sulfhydryl groups in the liver; sulfhydryl concentration in the kidney was reduced only at the higher dose. The authors attribute acrylonitrile's toxicity to inactivation of the sulfhydryl-dependent enzymes. As discussed in the Biotransformation Section (III-B-2) acrylonitrile has been shown to combine with sulfhydryl groups.

Dinu and Klein (1976) observed decreased sulfhydryl concentrations in rats poisoned with acrylonitrile. Male rats (90-120 g) injected with twice the LD_{50} (dose not specified) showed increased catalase activity in the liver, but not the kidney, compared to controls. In both the kidney and liver, lactic acid concentrations increased and nonprotein sulfhydryl decreased (Table 36). The authors suggest these biochemical changes may result in an accumulation of peroxide, which results in tissue damage.

Table 36

Catalase, Sulfhydryl and Lactic Acid Levels
in Rats Intoxicated with Acrylonitrile (Dinu
and Klein, 1976)

	Control	Experimental	P
Catalase[a]: liver	3.76 ± 0.18	4.56 ± 0.09	< 0.01
kidney	2.49 ± 0.18	2.48 ± 0.19	> 0.1
SH[b]: liver	421 ± 16.8	24 ± 1	< 0.01
kidney	250 ± 9.63	24.6 ± 0.6	< 0.01
Lactic Acid[c]: liver	9.62 ± 0.43	14.70 ± 0.94	< 0.01
kidney	7.35 ± 0.64	26.60 ± 1.60	< 0.01

[a] µmoles H_2O_2 decomposed/15 seconds/g tissue

[b] Nonprotein sulfhydryl; µmoles SH/100 g wet tissue

[c] mg/100 g tissue

Vainio and Mäkinen (1977) investigated acrylonitrile-induced depression of hepatic nonprotein sulfhydryl content. Rats, mice, guinea pigs and hamsters were treated intraperitoneally with 0, 20, 40, 60, or 80 mg/kg acrylonitrile (in 0.9% NaCl), then decapitated at varying time intervals. The nonprotein sulfhydryl groups were determined.

As shown in Table 37, acrylonitrile decreased the nonprotein sulfhydryl content at all concentrations in a dose related manner compared to controls. A dose of 80 mg/kg to hamsters, guinea pigs and rats resulted in 86.5%, 82.9% and 83.6% sulfhydryl depletion, respectively, after 1 hour compared to controls. In mice, 60 mg/kg (80 mg/kg not tested) resulted in 80.8% de-

Table 37

Effect of Acrylonitrile (administered i.p.) on the Hepatic Nonprotein Sulfhydryl Content of Various Species (Vainio and Mäkinen, 1977)

Dose (mg/kg)	Nonprotein Sulfhydryl Content (µmol/g liver w. wt.)[a]			
	Hamster[b,c]	Guinea Pig[d,c]	Rat[e,c]	Mouse[f]
0 (saline)	7.4	7.0	6.7	9.9
20	5.1	5.6	4.0	7.1
40	3.0	2.0	2.8	3.8
60	1.4	1.2	1.8	1.9
80	1.0	1.2	1.1	NR

NR = not reported

[a] the number of animals used per dose ranged between 2-4

[b] adult female Syrian golden hamsters; weight not reported

[c] killed 1 hour after AN administration

[d] adult males; 400-550 g

[e] adult male Sprague-Dawley rats; 160-300 g

[f] adult male GP-20 mice; 22-30 g; killed 0.5 hour after AN administration

pletion after 0.5 hours. Administration of 30 mg/kg in mice resulted in depletion within 15 minutes but this level rose after 2 hours.

Szabo et al. (1977) demonstrated lowered nonprotein sulfhydryl levels (expressed as reduced glutathione) in other tissues besides the liver. They showed 80 to 90% decreases in liver, lung and kidney glutathione within 5 minutes of acrylonitrile administration (15 mg/100 g i.v.) in female Sprague-Dawley rats. However, no specific tissue damage was detected. Cerebral and adrenal glutathione decreased more gradually and reached lowest levels after 60 and 15 minutes, respectively. Szabo et al. (1977) suggest acrylonitrile or its reactive (probably epoxy) derivative interacts with reduced glutathione.

Hashimoto and Kanai (1972) suggested the pyruvate oxidation system might be sensitive to acrylonitrile, possibly due to its reactivity with sulfhydryls. Male guinea pigs (400 ± 30 g) were used for *in vitro* experiments. Acrylonitrile (at a final concentration of 2×10^{-3} M or 2×10^{-2} M) was added to diluted blood and homogenized liver and brain tissue *in vitro*; sulfhydryl content was determined after 30 minutes. For *in vivo* experiments male guinea pigs and rabbits (2500 ± 250 g) were given 100 mg/kg, i.p., and 30 mg/kg, i.v., respectively, of a 5% solution of acrylonitrile in 0.9% saline solution. Sulfhydryl content was determined in both species. In addition, pyruvic and lactic acids were determined in guinea pigs.

In vitro, acrylonitrile resulted in a decrease of total sulfhydryl, especially nonprotein sulfhydryls. In blood, liver, and cerebral tissue, total sulfhydryl was only 83 to 47% of control values and nonprotein sulfhydryl was 75 to 7% of controls. Decreases were most marked in liver and cerebral tissue (Table 38).

Table 38

Effect of Acrylonitrile on Tissue Sulfhydryl
(Hashimoto and Kanai, 1972)[a]

		Treated as % of Controls	
		Guinea Pigs	Rabbits
Nonprotein SH[b]			
Blood		83	70
Liver		13*	18*
Cerebrum:	gray	51*	65*
	white	49	53*
Protein SH[c]			
Blood		53*	81
Liver		34*	104
Cerebrum:	gray	45*	57*
	white	53*	61*

*significantly less than control at $p < .05$ using raw data for control vs treated animals

[a] SH measured 1 hour after 100 mg/kg administered to guinea pigs and 30 mg/kg to rabbits

[b] number of animals per determination:
guinea pigs: 8 treated, 5 control
rabbits: 3-4 treated, 3-6 control

[c] guinea pigs: 6 treated, 5 control
rabbits: 3-4 treated, 3-6 control

In vivo, guinea pigs and rabbits showed significantly decreased nonprotein sulfhydryl in the liver and brain. Protein sulfhydryl was significantly decreased in the brain of rabbits and all tissues in guinea pigs (Table 38).

Seven determinations of sulfhydryl in blood were made over 270 minutes after AN administration in rabbits. Protein sulfhydryls in red cells initially decreased (lowest value occurred after about 20 minutes) but recovered within 1 hour. Nonprotein sulfhydryl, however, decreased more slowly (lowest value reached after 60 minutes) and recovered more slowly.

Tissue pyruvate and lactate were measured in guinea pigs 30 (3 animals) and 60 (6 animals) minutes after administration of 100 mg/kg acrylonitrile, and 60 minutes (5 animals) after giving a combination of acrylonitrile (100 mg/kg) and sodium thiosulfate (450 mg/kg). After 60 minutes, in guinea pigs receiving either treatment, significant increases were observed for pyruvate and lactate levels in the liver, blood and brain. Elevations in brain pyruvate were particularly marked.

Hashimoto and Kanai (1972) suggest that the excess level of pyruvate in the brain might have caused cerebral dysfunction. Since sodium thiosulfate did not prevent accumulation of pyruvate or lactate, they suggested the pyruvate oxidation system might be sensitive to acrylonitrile, possibly due to its reactivity with sulfhydryls.

e) Effect on the Circulatory System

Graczyk (1973) examined the effect of acrylonitrile administration (13, 27, 55 or 110 mg/kg i.v.) on the respiration and blood pressure of anesthetized rabbits given adrenaline, noradrenaline or acetylcholine.

Appropriate circulatory responses to these substances, although somewhat weakened, were maintained during acrylonitrile intoxication. It is unlikely, therefore, that the circulatory system is a major target system in acrylonitrile poisoning.

b. Subacute Toxicity

1) Inhalation Exposure

a) Signs

The effect of inhaling acrylonitrile vapors for 8 weeks (4 hours/day, 5 days/week has been described for several species by Dudley et al. (1942). A weighed amount of acrylonitrile was vaporized and introduced into an air current of known minute volume which was blown into a closed chamber. Generalized effects included weight loss, eye and nose irritation, or weakness. Signs varied among species, dose, and duration as described below.

In another subacute experiment, Brewer (1976) prepared a report for Industrial Bio-Test Laboratories, Inc., on a 90 day acrylonitrile vapor inhalation study in CD-1 mice, albino rats (Charles River) and Beagle dogs. Exposure, in 4.5 m^3 capacity chambers, was limited to 6 hours/day, 5 days/week for 13 weeks (total of 57 exposures) at about 0, 30, 60 or 120 ppm. Acrylonitrile vapor was mixed with clean dry air introduced into the chamber. Treated mice, rats, and dogs exhibited: ataxia, grooming, ptosis, emaciation, nausea, rhinitis and diuresis. Most animals experienced clonic convulsions prior to death. Mortality rates, which appear in Table 39, appear unusually high for control mice and rats.

Specific signs and growth effects in different species are described below:

Table 39

Mortality in Animals Exposed to Acrylonitrile
over 90 Days (57 6-hr exposures) (Brewer, 1976)

Species	Exposure (ppm)	Mortality Males	Mortality Females
Mice	0	10/15	4/15
	~ 24	8/15	12/15
	~ 54	8/15	6/15
	~108	14/15	13/15
Rats	0	2/20	4/20
	~ 24	4/20	1/20
	~ 54	3/20	2/20
	~108	12/20	6/20
Dogs	0	0/6	0/6
	~ 24	0/6	0/6
	~ 54	1/6	2/6

Rats. Charles River albino rats and CD-1 mice exposed to 30, 60 or 120 ppm (65, 130, or 260 mg/m^3)for 13 weeks (6 hr/day, 5 days/wk) showed no statistical growth rate impairment compared to controls (Brewer, 1976). However, weight data were analyzed only for those animals surviving the entire test period (Table 40), obviously masking possible weight reductions in animals who died.

Sixteen rats exposed to 220 mg/m^3 for 8 weeks (4 hr/day 5 days/wk) showed only slight lethargy during exposure (Dudley et al., 1942). Three females gave birth and raised normal litters. However, 16 rats (8 adults, 8 young animals; sex and weight not reported) exposed to 330 mg/m^3 in the same manner showed weight loss and poor physical health. All 8 young rats showed growth impairment (no data are presented) and nasal and eye irritation; 5 had died by the sixth week of exposure (Dudley et al., 1942).

Guinea Pigs. Sixteen guinea pigs exposed to 220 mg/m^3 for 8 weeks (4 hr/day, 5 days/wk) showed slight lethargy during exposure but otherwise exhibited no toxic effects and even gained weight. Sixteen guinea pigs exposed similarly to 330 mg/m^3 initially showed eye and nose irritation, and salivation; 3 died during the fifth week (Dudley, et al., 1942).

Rabbits. Three rabbits exposed to acrylonitrile at 220 mg/m^3 for 8 weeks (4 hours/day, 5 days/week) were listless during exposure and failed to gain weight. When 4 rabbits were exposed to 330 mg/m^3 in the same way there was moderate irritation of the eyes and nose; one died during the fifth week (Dudley et al., 1942).

Cats. Four cats exposed for 8 weeks (4 hours/day, 5 days/week) to 220 mg/m^3 acrylonitrile suffered from vomiting, listlessness, and weight loss. One cat developed transitory hind leg weakness after the third exposure and died during the third week. Four cats exposed to 330 mg/kg (in the same way) were in severe distress; all developed transitory hind leg weakness and irritation of the nose and eyes (Dudley et al., 1942).

Dogs. Two dogs (breed, sex, age, and weight not specified) were to be exposed for 4 hours/day, 5 days/week for a 4 week period to 120 mg/m^3 acrylonitrile. One dog died four hours after the first exposure; death was preceded by convulsions. The second dog became weak after the 5th, 13th, and 14th exposures but otherwise tolerated all others (Dudley et al., 1942).

Beagles surviving acrylonitrile exposure (30, 60 or 120 ppm) for 13 weeks showed no growth impairment compared to controls (Brewer, 1976).

Monkeys. Four rhesus monkeys (age, sex and weight not reported) showed no toxic effects when exposed to 120 mg/m^3 of acrylonitrile in a closed chamber for 4 hours/day, 5 days/week for 4 weeks. Two rhesus monkeys exposed to 330 mg/m^{3}for 4 hours/day, 5 days/week over 8 weeks exhibited sleepiness and weakness, appetite loss, salivation, and vomiting. One monkey died after 6 weeks of exposure; the second monkey was in collapse after each exposure during the last 2 weeks (Dudley et al., 1942).

b) Hematological Effects

With respect to total leukocyte count, differential leukocyte count, erythrocyte count, hemoglobin concentration, hematocrit or erythrocyte indices, there were no alterations in dogs or rats (data from 3-10 animals/dose/sex) exposed to 0, 30, 60 or 120 ppm AN for 13 weeks (Brewer, 1976). Treated rats had elevated blood thiocyanate levels and elevated non-protein free sulfhydryl content. These parameters were unaffected in dogs. Urinalyses were normal for treated rats and dogs.

Weekly red blood counts, white blood counts and hemoglobin levels were within normal ranges while eosinophile counts were increased in 4 rats and 4 rabbits exposed to 330 mg/m^3 of acrylonitrile for 8 weeks (4 hours/day, 5 days/week) (Dudley et al., 1942).

Minami et al. (1973) exposed 8 male rabbits to 20 ppm (54 mg/m^3) acrylonitrile for 1 day (8 hours) a week for 8 weeks. Before and after each exposure, 3 ml of blood from the auricular vein were analyzed for:

pO_2, pCO_2, pH, cyanide and thiocyanate ions, hemoglobin, and hematocrit (Table 40). When values for all 8 exposures are summed, pO_2, pH and thiocyanate ions were significantly increased while PCO_2 was significantly decreased compared to pre-exposure levels.

c) Pathology

Organ weights of mice, rats and dogs exposed for 13 weeks (6 hours/day, 5 days/week) to a maximum of 120 ppm were within normal units (Brewer, 1976). Organ weights of liver, kidney, spleen, pituitary gland, lungs, gonads, thyroid gland, adrenal gland, heart and brain were determined.

Examination of tissue in treated dogs revealed treatment-associated changes in the lung. These alterations consisted of focal aggregates of alveolar macrophages in alveolar lumina, indicative of the irritative effect of acrylonitrile.

Dudley examined tissue in animals exposed to 220 or 330 mg AN/1 for 8 weeks (4 hours/day, 5 days/week). A total of 680 sections were made (18 rats, 6 rabbits, 6 cats, 16 guinea pigs, 1 monkey) and these changes were observed:

Spleen	slight hemosiderosis in rats (indicates blood destruction) and negligible hemosiderosis in cats, guinea pigs, rabbits.
Kidney	renal irritation hyaline casts in straight collecting tubules of most individuals subacute interstitial nephritis (but not extensive), especially in guinea pigs and rabbits
Liver	damage in cats only

Table 40

Hematological Values (venous blood) in Rabbits
Before and After Exposure to 20 ppm Acrylonitrile[a]
(Minami et al., 1973)

	Before	After	$P_{.05}$ (15)
pO_2	70.6 ± 7.35	80.56 ± 4.75	$p < .01$
pCO_2	35.2 ± 1.42	31.15 ± 2.96	$p < .01$
pH	7.397 ± .0180	7.437 ± .0193	$p < .001$
Cyanide ions (μg/ml)	0.165 ± .060	0.1825 ± .034	n.s.
Thiocyanate ions (μg/ml)	1.937 ± .120	2.919 ± .403	$p < .001$
Hemoglobin (g/dl)	12.59 ± 0.36	12.33 ± .50	n.s.
Hematocrit (%)	42.14 ± 1.61	40.91 ± 1.85	n.s.

[a] exposure for 8 hr/day/week for 8 weeks;
each value represents average (± S.D.) of 8 exposures
[calculated by LMM]

Lung	subacute bronchopneumonia: congestion and edema of alveolar walls, extravasion of red cells and serum into alveoli, focal collection lymphocytes and polymorphonuclear leukocytes in most guinea pigs, rabbits, the monkey and 1/3 of the rats.

2) Oral Administration

a) No Effect Level

Ingestion of various doses of acrylonitrile was without effect in adult albino rats (Porton strain; sex and weight not reported). Over a period of 7 weeks, 6 rats were given 15 successive daily doses of 30 mg/kg, and then 7 doses of 50 mg/kg, followed by 13 doses of 75 mg/kg. Gait, stance (both as a measure of nervous system and muscle toxicity), and weekly weights were unaffected (Barnes, 1970).

Incorporation of 85 ppm or less of acrylonitrile into the drinking water for 90 days had no effect on male or female Sprague-Dawley rats (Humiston et al., 1975; sponsored by the Manufacturing Chemists Association). Details of the parameters measured appear in the subsections that follow.

b) Effect on Weight Gain

Fifteen male and 15 female Sprague-Dawley Spartan substrain SPF-derived rats (6-7 weeks old) each received 0, 35, 85, 210 or 500 ppm AN in the drinking water (equivalent to 0, 4, 10, 25 or 60 mg/kg) (Humiston et al., 1975). The dosage of acrylonitrile ($\bar{x}$ ± S.D.) calculated from actual water consumption was 0, 4 ± 1, 8 ± 2, 17 ± 3 or 38 ± 8 mg/kg for males and 5 ± 1, 10 ± 1, 22 ± 2 or 42 ± 4 mg/kg for females.

Appearance and demeanor were unchanged. Males at 500 ppm showed significantly depressed body weight gains throughout the 90 days, while females at 210 and 500 ppm showed significant weight gain depression only after day 57. All other rats exhibited normal growth.

Mean weekly food consumption by males receiving 210 or 500 ppm was significantly decreased for a total of 2 and 7 weeks, respectively, out of 9 weeks for which data were presented (weeks 10, 11, and 12 were during the mating period). Female rats receiving 210 or 500 ppm showed decreased consumption for 6 and 1 weeks, respectively, out of 13 weeks.

Water consumption was significantly decreased for males and females receiving 85, 210 or 500 ppm AN. Rats often will refuse to drink adverse water, which will cause a decrease in food consumption. Weight gain, therefore, is not always a good measure of the toxic effects of chemicals administered in the drinking water.

c) Effect on Clinical Parameters

As part of a 90 day study incorporating acrylonitrile in the drinking water of rats, Humiston et al. (1975) evaluated blood, urine and serum.

Hematological evaluations of 5 rats/sex receiving acrylonitrile at 0 or 500 ppm for 83 days were performed for packed cell volume, red blood cell count, hemoglobin concentration, white blood cell count and differential leucocyte count. Values for males were within normal limits. Females had a statistically significant decrease in red blood cell count but were otherwise normal.

Although urine pH, sugar, proteins, occult blood and bilirubin were normal in rats receiving 500 ppm AN in the drinking water, urine specific gravity was increased significantly the last week of the study. On day 90 males receiving 210 ppm and females receiving 85 ppm also had a higher specific gravity, the increase being attributed to decreased water consumption (Humiston et al., 1975).

With respect to blood urea nitrogen and alkaline phosphatase levels in 10 male rats receiving 500 ppm AN, there were significantly higher values than controls but serum glutamic pyruvic transaminase activity was normal. Hematological chemistry values for all other rats were normal.

d) Effect on Organ Weights

Significant changes in absolute and relative organ weights were seen among some rats receiving acrylonitrile in the drinking water for 90 days:

35 ppm	no changes
85 ppm	females: lower absolute brain weight and higher relative liver weight (however, this increase was accounted for by one rat with an unusually large liver).
210 ppm	females: lower absolute brain weight and higher relative liver weight; males: higher relative liver weight.
500 ppm	females: higher relative liver weight; males: higher relative liver and kidney weights.

e) Pathology

Gross examination revealed no pathologic alterations related to acrylonitrile ingestion (in the drinking water) for 90 days (Humiston et al., 1975). One male rat (receiving 210 ppm) had a small subcutaneous tumor in the abdominal area possibly of mammary gland origin. The authors consider the tumor to be of spontaneous occurrence.

Microscopic tissue examination revealed one male rat (at 500 ppm AN) with a microfocus of intraepithelial necrosis and edema in the non-glandular portion of the stomach, considered to be of spontaneous origin (Humiston et al., 1975).

f) Effect on the Adrenals

Szabo et al. (1976) reported that for rats, acrylonitrile at 0.05 or 0.2% in the drinking water (500 or 2000 ppm) for 21 to 60 days affects the mineral corticoid and glucocorticoid producing cells of the adrenal cortex. Female Sprague-Dawley rats (200 g; number not specified) were sacrificed 7, 21 or 60 days into the treatment. Rats on both levels of acrylonitrile had reduced water intake (3/4 of control) and urine output (1/3 of control); body weights were slightly reduced during the first week and growth was only mildly retarded thereafter.

After 21 or 60 days, the adrenals of treated rats showed an atrophic zona fasciculata but an increased zona glomerulosa. After 21 days at the higher acrylonitrile dose, plasma Na^+ (but not plasma K^+) was significantly increased by 9 mEq/liter. These rats had a reduced plasma corticosterone concentration (24 ug lower than controls).

g) Effect on Glutathione

Female Charles River (Sprague-Dawley derived) rats were given 20, 100, or 500 ppm acrylonitrile in the drinking water or by gavage (.002, .01, or .05% AN, respectively) for 21 days (Szabo et al., 1977). These doses were shown previously to cause adrenocortical hypofunction (refer to preceding section). Dose dependent increases in liver glutathione levels were observed and were more marked when the dose was administered by gavage (Table 41). Increased glutathione had been described previously for chemical carcinogens. The authors maintained "it remains to be seen whether these changes correlate" with lesions reported for brain and stomach tissue in rats fed acrylonitrile or with the higher mortality levels among factory workers exposed to acrylonitrile.

Table 41

Effect of AN Administration (21 days) on Hepatic Glutathione in Rats by 2 Routes of Administration (Szabo et al., 1977)

	Glutathione (μg/g liver)
Control	1431.14 ± 24.08
Acrylonitrile 0.002%	
-drinking water	1506.00 ± 85.29
-bolus	1535.84 ± 14.44*
Acrylonitrile 0.01%	
-drinking water	1492.01 ± 75.59
-bolus	1621.45 ± 26.14**
Acrylonitrile 0.05%	
-drinking water	1666.00 ± 68.16**
-bolus	1782.02 ± 84.29**

Mean ± standard error of mean. Student's t-test.
* = $p < 0.05$; ** = $p < 0.005$, as compared to control

The increased hepatic glutathione reported was in direct contrast to decreased hepatic glutathione levels in acute experiments (Szabo et al., 1977; see section on Acute Percutaneous Administration).

h) Effects on Reproduction

Murray et al. (1976) reported adverse maternal and fetal effects after pregnant rats were fed 25 or 65 mg AN/kg/day during gestation. Schuefler (1976) found AN to be embryotoxic to pregnant mice. Details of these studies are reported elsewhere (Section IV-C).

3) Percutaneous Administration

The effects of subacute administration by injection have been described for central nervous system and organ changes.

a) Effect on the Nervous System

The effect of acrylonitrile on Y-maze performance in rats was carried out by Krysiak and Knobloch (1971) as a measure of central nervous system function. Prior to acrylonitrile administration rats were trained for performance in the maze. Rats given daily i.p. doses of 20 mg AN/kg over 6 weeks or daily s.c. doses of 40 mg AN/kg over 4 weeks showed a significant lengthening of time to perform correctly in the maze and a decrease in the number of correct reactions compared to pre-treatment observations or controls. Performance improved after treatment was discontinued.

b) Effects on Organs

Daily i.p. administration of 50 mg AN/kg over 3 weeks in adult Wistar rats caused statistically significant body weight loss, leukocytosis, and a significant increase in serum asparagine aminotransferase (Knobloch et al., 1971). The absolute weights of the heart and liver (but not the brain, lungs, kidneys or spleen) were increased significantly. The relative weights (organ weight per 100 g body weight) were significantly increased for the heart, liver, kidneys, and spleen. Examination of tissues revealed slight damage to neuronal cells of the cortex and brain stem; the liver and kidneys showed parenchymal degeneration.

Daily s.c. administration of 5 mg/kg acrylonitrile to rats for 10 days resulted in decreased total protein content of the liver for 40 days and of the blood for 70 days (Solovei, 1974). The author suggests acrylonitrile administration may result in decreased liver protein synthesis.

c. Chronic Toxicity

Long-term studies have been conducted for two routes of administration: inhalation exposure in rats and rabbits and oral administration in rats and dogs. Maltoni et al. (1977) have recently completed a 2 year carcinogenicity bioassay on rats exposed to AN by gavage and inhalation; these studies are discussed in section IV-D.

1) Inhalation Exposure

A two year inhalation study, sponsored by the Manufacturing Chemists Association, was recently completed (Jan. 18, 1978). Male and female rats were exposed to 0, 20, or 80 ppm of acrylonitrile (6 hours/day, 5 days/week). Microscopic tissue examination has not been completed. Based on a gross pathologic examination of rats exposed to 80 ppm, there was an increase in the incidence of ear canal tumors in males and females, of the gastrointestinal tract in males and of the mammary region in females. Female rats exposed to the lower level (20 ppm) showed an increase of subcutaneous mammary region tumors. Preliminary microscopic examinations revealed an increase of brain tumors at both exposure levels (Clark, 1978). No other details are available at this time.

Knobloch et al. (1972) exposed male and female Wistar rats and albino rabbits to acrylonitrile vapors at concentrations of 0, 250 or 500 mg/m^3

over 6 months. Exposure was for 3 hours/day, 6 days/week for 6 months. Throughout the period, body weight gain was significantly reduced for 4 out of 11 weeks in rats subjected to 500 mg/m^3 AN. Rats at the lower concentration showed normal weight gain.

The number of eosinophiles was significantly reduced in treated rats after 4 months of the experiment (Table 42). Total blood protein was unchanged. However, albumin, α-globulin and γ-globulin were significantly increased (Table 42). Kidney dysfunction in rats was suggested by these changes: increased diuresis at both concentrations, increased urinary protein at the higher concentration, and areas of degenerated proximal convoluted tubules at the higher concentration.

Cardiovascular damage in treated rabbits was indicated by statistically significant decreased blood pressure compared to controls at the termination of the experiment. In rabbits exposed to the higher concentration, there was a significant increase in the weight of the heart.

Inflammation of the pulmonary system accompanied by an inflammatory exudate in the bronchial lumen occurred in rats exposed to 250 mg/m^3.

2) Oral Administration

Several studies have been conducted on the effects of long-term feeding of acrylonitrile; three of these are unpublished. In one, Tullar (1947) administered acrylonitrile to male rats for two years. Growth retardation was observed, along with possible tumorigenicity. The FDA (Kennedy, 1977), however, described the study as "inadequate by contemporary standards" because of the small sample size, the use of male animals only, and the "failure to use a full range of toxicological criteria". For completeness,

Table 42

Changes in Wistar Rats After Exposure to Acrylonitrile (0, 50 or 250 mg/m^3) for 3 Hours/Day, 6 Days/Week for 6 Months[a] (Knobloch et al., 1972)

	Control	50 mg/m^3	250 mg/m^3
Eosinophiles (n):			
mo. 0	90	100	120
mo. 5	400	1010*	700*
Total blood protein (g%)			
mo. 2	6.28	6.45	6.13
Albumin (g%)			
mo. 2	2.98	3.32*	3.25*
Globulin (g%)			
mo. 2			
α_1	0.64	0.91*	0.81*
α_2	0.61	0.63	0.53
β	1.36	1.17	1.16
γ	0.64	0.42*	0.38*
Diuresis (ml/urine/24 hr)			
mo. 2	6.9	10.1*	15.0*
Urinary protein (mg/24 hr)			
mo. 2	17.16	17.16	21.87*
Body wt.[b] (g increase)			
wk 10	120	125	85
wk 20	160	175*	140*

*significant difference between experimental and control groups

[a] some values estimated from charts and graphs in text

[b] age 1.5 mo.; initial body weight 110-150 g

Tullar's (1947) data on growth are presented in this section.

Another long-term feeding study on rats is in progress; results after 13 months are currently available. Marked toxicity was observed in rats ingesting 100 or 300 ppm acrylonitrile contained in the diet.

A third study assesses the toxicity of acrylonitrile administered over 6 months to beagle dogs; marked toxicity occurred at 200 or 300 ppm AN. A discussion of these studies follows.

a) Effect on Rats

Tullar (1947) orally administered acrylonitrile to male albino rats for 2 years. Groups of 20 animals were allocated according to the following design:

Group A, normal control; food and water ad lib.

Group B, paired control for group C

Group C, unlimited water containing 0.05% v/v AN; unlimited food

Group D, unlimited food fumigated with AN; unlimited water.
(25 cc AN added to a drum containing five/1 kg sacks of
meal. Drum sealed for 24 hours, then exposed to air
for at least 10 days)

Rats were individually housed; weekly records were made of body weights and food and water consumption. Average weights, at 5 week intervals, appear in Table 43. Acrylonitrile in the drinking water (Group C) retarded growth consistently from the controls (Groups A and B) and food-treated rats (Group D).

After two years, total mortality was higher in treated-water rats (50%) than paired controls (25%), normal controls (15%) or food-treated rats (5%). Weight gain in rats given acrylonitrile in the food almost

Table 43

Effect of Long-Term Oral Feeding of Acrylonitrile in Rats (Tullar, 1947)[a]

Weeks of Treatment	A Control Av. Wt. (g)	N	B Paired-Control For Group C Av. Wt. (g)	N	C 0.05% AN in drinking water Av. Wt. (g)	N	D AN fumigated food Av. Wt. (g)	N
0	63	20	63	20	62	20	67	20
5	194		179		157	19	197	
10	280		254		238		281	
15	312		292		267		307	
20	329		310		282		324	
25	338		322		287		331	
30	343		331		295		336	
35	366		344		317		352	
40	383		369		331		366	
45	388		376		339		377	
50	394		383		340		381	
55	398		390		345		384	
60	405	19	381		364		395	
65	412		379		347	18	400	19
70	405		376	19	355	16	395	
75	411		387	17	354		391	
80.6	404		376		347		394	
85	400	18	374		343	15	388	
90	409	17	390	16	348	14	391	
95	407		388	15	334		373	
100	416		397		336	13	397	
105	413		386		336	10	404	

[a] data in original reference are presented weekly

reached the weight gain by controls, but was always slightly less. Tullar (1947) concluded that food fumigated with acrylonitrile, unlike water-treated acrylonitrile, does not retard growth or the life span of rats, indicating a lack of cumulative effects.

A separate study by Tullar (1947) was the basis on which methods and dosages were determined for the chronic study just discussed. A higher dose of AN in the drinking water (0.1%) was not tolerated for 13 weeks (82% weight gain during this period compared to 237% gain in paired controls). However, complete recovery of growth followed withdrawal of acrylonitrile.

In another long-term study, Ferin et al. (1961) incorporated 0.1% (1000 ppm) or 0.002% (20 ppm) acrylonitrile in the drinking water of 100 rats (strain or sex not specified) for six months. Effects on rats at the higher dose included increased leukocyte counts and increased relative liver, spleen, and kidney weights. At the lower dose, functional changes in the central nervous system (based on a "memory test") and in the detoxification function of the liver were noted. However, data are sparse, making interpretation difficult.

Svirbely and Floyd (1961) administered acrylonitrile at 0.5, 5.0 and 50 ppm in the drinking water of male and female CFW rats for 2 years. Average drinking water consumption was slightly decreased at the highest level for both sexes, possibly related to the odor threshold of AN (10 ppm in humans). Periodic (not specified by authors) hematological observations indicated normal values for hematocrit, hemoglobin, white blood cells, and differential count. Cumulative mortality in treated rats was within the range of controls as the data on the following page show.

Organ weights were reported as with within normal ranges. However, data presented in this paper are sparse and make evaluation of the results difficult.

Cumulative Mortality

Dose (ppm)	Males/Females[a] Weeks of Test 3	6	12	24	48	52	96	104
0	0/0	0/0	0/0	0/0	1/1	1/1	8/3	9/6
0.5	0/0	1/0	2/0	3/0	3/0	4/0	8/0	9/1
5.0	0/1	0/1	0/1	0/1	0/2	0/2	4/9	5/11
50.0	0/0	0/0	0/0	0/0	0/0	0/0	2/8	3/9

[a] 25 rats per level per sex

A 13-month status report on a 24 month study (sponsored by the Manufacturing Chemists Association) incorporating acrylonitrile in the drinking water was issued by Norris (1977) and, in more detail, by Quast et al., (1977). Acrylonitrile was incorporated into the drinking water of Sprague-Dawley (SPF derived) rats at 0, 35, 100, or 300 ppm acrylonitrile (equivalent to 0, 4, 10 or 30 mg/kg body weight/day, respectively). Rats were initially 6 to 7 weeks old; males weighed about 310 g and females weighed about 210 g. Ten rats/sex/dose were sacrificed after 12 months.

Statistically significant reductions in body weights at 35, 100 and 300 ppm were associated with dose-related decreased water consumption, and decreased food consumption at 300 ppm (females consumed less food at 100 ppm also) (Table 44). The following other data were obtained:

Hematological and Urinary Effects. Hematological evaluations and urinalyses were performed on day 353 for males (8-10/dose) and on day 354 for females (7-10/dose). There were no significant differences compared to controls for: packed cell volume, red blood cell count,

Table 44

Acrylonitrile in the Drinking Water of Rats

The number of times food or water or weight was significantly ($p < .05$) decreased from control values during 12 months (Quast et al., 1977) (numerator=no. times parameter decreased; denominator=no. times parameter measured)

PPM AN in Water	Food[a]		Water[b]		Weight[c]	
	Male	Female	Male	Female	Male	Female
35	0/20	5/20	11/22	18/22	0/13[d]	9/12
100	2/20	7/20	22/22	21/22	7/13	12/12
300	10/20	11/20	22/22	22/22	13/13	12/12

[a] based on food consumed by 24-30 rats/sex/dose

[b] based on water consumed by 21-30 rats/sex/dose

[c] based on weight of 10 rats/sex/dose

[d] after 100 days there was a statistically significant trend toward reduced body weight (repeated measures analysis of variance)

hemoglobin concentration, white blood cell count or differential leukocyte count. No differences were found in urine for: pH, sugar, protein, ketones, bilirubin, occult blood, or urobilinogen. Males maintained at 300 ppm and females at 100 or 300 ppm had a significantly increased urine specific gravity.

Blood urea nitrogen (BUN), alkaline phosphatase (AP) activity and serum glutamic pyruvic transaminase (SGPT) activity were measured on day 368 in fasted rats. AP was significantly increased in females receiving 300 ppm. All other values were within normal limits.

Gross Pathology. On day 368 fasted rats were sacrificed for autopsy. Organ weights were recorded and tissues were fixed and examined by standard methods.

The organ to body weight ratios (g tissue/100 g bw) were significantly increased for heart, liver, and brain in males and for liver and kidney in females receiving 300 ppm. Males receiving 100 ppm showed significantly increased body weight ratios for the brain only; females at 100 ppm had significantly lower heart weights. Body weights of fasted males and females at 300 or 100 ppm were significantly lower than control weights.

Based on 10 males and 9-10 females sacrificed per dose the percent occurrence of pathologic findings are summarized in Table 45. Males and females at the two higher doses developed lesions in the non-glandular portion of the stomach which were characterized by paleness and thickening of the mucosa, erosions, ulcers and, sometimes, papilloma formations. Three females at 300 and 100 ppm and 1 male at 300 ppm had ear canal tumors. Other, less clearly dose related changes appear in Table 45.

Microscopic findings of tissues with tumorous changes revealed increased frequency of gastric cell papillomas, Zymbal (sebaceous) gland tumors of the ear canal and microtumors of the nervous system in rats receiving 100 or 300 ppm only. The squamous cell papilloma in the stomach is seen only infrequently in this strain of rat as a spontaneous occurrence. Zymbal gland tumors do occur spontaneously in this strain but the high frequency in treated rats is considered significant.

The nervous system changes (possibly of mesodermal origin) suggest perivascular location at this time. As the lesion advances it appears to invade brain tissue. Advanced tumors had a sarcomatous appearance. Due to the small sample size the low occurrence of other tumors can only suggest treatment related effects.

Microscopic nontumorous changes include minimal hepatic lesions in rats receiving 100 or 300 ppm (possibly related to the decreased nutri-

Table 45

Gross Pathologic Findings in Male and Female Rats Maintained on Water Containing AN for 12 Months (Quast et al., 1977)

	Concentration of AN in the Water (ppm)			
GROSS PATHOLOGIC FINDINGS	0	35	100	300
Number of rats sacrificed	10/9[a]	10/9	10/10	10/10
Gastrointestinal Tract				
Stomach - nonglandular portion				
Pale Thickened foci	0/0	0/0	1/2	3/3
Focal gastric papilloma(s)	0/0	0/0	0/0	7/5
Gastric erosion or ulcer	0/-[b]	0/-	1/-	1/-
Small intestine tumor	0/-	0/-	2/-	0/-
Large intestine tumor	0/-	0/-	0/-	0/-
Decreased amount of intraabdominal fat	0/-	0/-	2/-	6/-
Kidneys				
Pitting of the cortex	3/0	1/0	2/0	1/1
Focal scar formation in the cortex	2/-	2/-	1/1	1/-
Mineral deposit within the pelvis	3/-	2/-	0/-	1/-
Dilated pelvis	1/2	3/0	0/0	1/0
Pale-colored foci in the cortex	0/-	1/-	1/-	0/-
Unilateral tumor	0/-	0/-	1/-	0/-
Liver				
Pale foci suggestive of necrosis	0/-	0/2	1/2	0/-
Clear fluid cyst in caudate lobe	-/0	-/1	-/0	-/1
Testes and Epididymis				
Unilateral testicular edema	0/-	2/-	1/-	0/-
Fat necrosis of epididymal fat pad	0/-	0/-	1/-	1/-
Eyes				
Focal corneal cloudiness	1/2	3/1	3/0	2/1
Focal lenticular opacity	1/0	0/0	0/0	1/1
Lungs				
Pale-colored foci	1/0	0/0	0/1	0/0
Epidermal Inclusion Cyst	0/-	0/-	0/-	1/-
Ear Canal Tumor, Unilateral	0/0	0/0	0/2	1/1
Spleen - increased in size suggestive of extramedullary hematopoiesis	0/0	0/0	0/0	1/1
Clitoral Gland Abscess	-/1	-/0	-/0	-/0
Tongue - 1 mm Sized Pale Foci on the Surface Near the Base	-/0	-/0	-/2	-/1
Subcutaneous Tumor in the Mammary Region	-/2	-/0	-/3	-/3
Subcutaneous Mammary Gland Hyperplasia	-/2	-/2	-/1	-/2

[a] number of rats affected: Male/Females

[b] dashes indicate data not reported

tional state), chronic renal disease in females receiving 300 ppm, and hyperplasia and hyperkeratosis of the squamous epithelium of the stomach receiving 100 or 300 ppm.

Quast et al. (1977) stress that it still remains to be seen "whether the tumorgenic activity of acrylonitrile can be differentiated from other manifestations of toxicity".

b) Effect on Dogs

Purebred beagle dogs were used in a 6 month oral toxicity study sponsored by the Manufacturing Chemists Association (Quast et al., 1975). Eight animals (4/sex) were given acrylonitrile in the drinking water at 0, 100, 200, or 300 ppm, which corresponds to the following doses (based on body weight and water consumption):

	$\bar{x}$ mg/kg ± SD	
ppm	Males	Females
100	10 ± 1	8 ± 1
200	16 ± 2	17 ± 2
300	17 ± 4	18 ± 5

Mortality and Toxic Symptoms. No controls or dogs at 100 m /kg died during the study. Five dogs at each of the two highest doses died spontaneously or were euthanized due to their debilitated state. Early signs of toxicity included decreased water and food consumption, decreased body weight, roughened hair coat, cough, and, later, wretching and vomiting. Terminal signs of depression, lethargy, weakness, emaciation and respiratory distress were noted.

Food and Water Consumption; Body Weight. Daily water consumption was averaged (by sex) at weekly intervals and compared to control. Water intake of dogs at 300 ppm was significantly lower 21 out of 26 weeks for males and 22 out of 26 weeks for females. At lower doses, drinking was essentially normal. At 200 ppm water ingested was significantly lower for only 1 week for males and 7 weeks for females. At 100 ppm, water consumption was higher 7 weeks for males and lower 1 week for females.

Daily food intake was averaged for each week, by sex, then an overall average was computed for all 26 weeks. Males at 300 and females at all concentrations showed a significant overall decreased food consumption, whereas males at 200 and 100 showed a significant increase.

Dogs that died or were euthanized showed progressive weight loss. In surviving animals, few significant weight differences were detected.

Ocular Lesions. Slit lamp ophthalmoscopic examinations conducted on 4 occasions revealed no eye lesions related to acrylonitrile exposure.

Hematologic Values. The following tests were made 8 days before, and on days 83, 130 and 179 during the investigation: packed cell volume (PCV); hemoglobin concentration (Hgb); red blood cell (RBC) and white blood cell (WBC) counts. No significant differences were apparent before testing. On day 83, males at 300 ppm showed significant decreases in PCV, RBC count and Hgb; males at 200 ppm showed a decreased RBC count. At day 83, females on 300 ppm showed a significant decrease in RBC count. All values were within normal ranges at days 130 and 179, except that females at 300 ppm on day 30 had a significantly lower RBC count.

Urinalyses. Urine samples were collected 8 days before, and at days 84, 135 and 176 during treatment, and at necropsy. Parameters determined were: specific gravity, pH, sugar, protein, ketones, occult blood, and bilirubin. All values were within normal limits.

Hematological Chemistry Values. Blood urea nitrogen (BUN), serum alkaline phosphatase activity (AP), serum glutamic pyruvic transaminase activity (SGPT) and serum glutamic oxaloacetic transaminase activity (SGOT) were measured 8 days before treatment and on days 84, 135 and 176. Males consuming all concentrations of acrylonitrile were always within normal limits. Females at 300 and 200 ppm showed a significant increase in SGOT activity at day 135; females at 200 ppm also showed decreased SGPT activity.

There was no significant change in liver or kidney nonprotein sulfhydryl content at 6 months for dogs at 100 ppm. No differences were apparent at the higher dosages, but sample sizes were too small to permit analysis.

No differences were detected on day 155 for total protein, albumin, and α_1, α_2, β or γ globulin values between control and treated dogs.

Pathology. Dogs surviving until termination of treatment (males, day 182; females, day 183) were fasted overnight and then exsanguinated. The brain, heart, liver, and kidneys were weighed in all animals; testes weights were determined in males. Weights for dogs at 100 ppm were normal. At 200 ppm, males (N = 2) had a significantly lower absolute brain weight, but had a higher kidney/body weight ratio compared to controls (N = 4). Data were obtained for only 1 male at 300 ppm and 1 female at 200 ppm, so statistical analysis was not possible. Females at 300 ppm (N = 2) showed a significantly lower brain/body weight ratio compared to controls.

Gross and histopathological changes in dogs receiving 100 ppm were comparable to control dogs. Foreign body pneumonia, a result of aspiration of food particles and lung nematodes, was a consistent finding in dogs receiving 200 or 300 ppm. The pneumonia was associated with gross and microscopic changes in the tongue and esophagus; the authors suggest AN in the drinking water might have irritated mucous membranes of the tongue and esophagus so swallowing was abnormal, resulting in aspiration of food.

4. Mechanism of Toxicity

There has been considerable disagreement about the mechanism of acrylonitrile intoxication. Some authors have proposed that the toxic action is due solely to the liberation of cyanide (which would inhibit cellular respiration), citing the similarity of symptoms to cyanide poisoning or the presence of cyanide or thiocyanate (Dudley and Neal, 1942; Dudley et al., 1942; Brieger et al., 1952). Other authors deny cyanide is involved at all (Paulet et al., 1966). A more prevalent opinion is that the effect of acrylonitrile is due in part to the liberation of cyanide, but mostly to direct effects of acrylonitrile. There may be substantial differences in the mechanism of toxicity between species.

a. Action of Cyanide

Although Dudley and his coworkers (Dudley and Neal 1942; Dudley et al., 1942), and others (Brieger et al., 1952) demonstrated the presence of cyanide or thiocyanate in animals acutely intoxicated with acrylonitrile, they did not adequately demonstrate that lethal concentrations of cyanide had been liberated. Several approaches have been taken to assess the role of cyanide in acrylonitrile intoxication, including: measurement of CN-metalloprotein complexes; effect on cytochrome oxidase; effect of cyanide antidotes.

1) Cyanide-Metalloprotein Formation

Cyanide intoxication is characterized by the formation of cyanide-metalloprotein complexes. Magos (1962) measured complex formation in rats intoxicated with acrylonitrile and concluded that the mechanism of toxicity is not solely due to cyanide liberation.

Cyanide-metalloprotein formation was estimated by determining methemoglobin and methemoglobin-CN formation (Magos, 1962). Groups of 10 male albino rats were injected subcutaneously with cyanide compounds (AN, potassium cyanide, acetone cyanohydrin) (dosage: LD_{50} x 1.5). Some animals from each group were also given 30 mg sodium nitrite (i.p.) 30 minutes before treatment to increase methemoglobin levels. Dosage schedules and mortality are presented below:

		Mortality	
Compound	Dose millimole/kg	without sodium nitrite	with sodium nitrite
acrylonitrile	2.8	5/5	5/5
potassium cyanide	2.4×10^{-1}	5/5	1/5
potassium cyanide	3.7×10^{-1}	-	4/4
acetone cyanohydrin	1.6×10^{-1}	5/5	0/5

Blood samples from rats given sodium nitrite to determine methemoglobin-CN levels were taken at death or 1 hour after injection of the cyanide. The optical density of the blood sample (hemolyzed and centrifuged) was read spectrophotometrically before and after addition of a drop of 20% potassium ferricyanide. A drop of 10% acetone cyanohydrin was added to the sample to convert methemoglobin to methemoglobin-CN and the optical density was read again; the decrease in density was inversely proportional to the original methemoglobin-CN concentration. Total hemoglobin as methemoglobin-CN after dilution with buffer and addition of ammonium hydroxide. These results were obtained:

	Compound	N	Time of Sample	Meth-CN: total Meth. ($\bar{x}$ ± S. D.)
1.	Acrylonitrile	5	at death	55 ± 8
2.	Potassium cyanide	5	at death	85.6 ± 8.7
3.	Acetone cyanohydrin or potassium cyanide	9	1 hour after cyanide injection	72.4 ± 12.7

The rate of methemoglobin-CN formation in rats given acrylonitrile (group 1) was significantly lower than rats killed by potassium cyanide (group 2; $t = 3.99$, $p < .002$) or rats surviving acetone cyanohydrin or potassium cyanide (group 3; $t = 2.21$, $p < .02$). These data lend weight to the view that the toxicity of acrylonitrile in rats is not due solely to the liberation of cyanide.

2) Effect on Cytochrome Oxidase

In cyanide poisoning inhibition of the enzyme cytochrome oxidase occurs.

Tarkowski (1968), however, determined that cytochrome oxidase was unaffected in rats intoxicated with acrylonitrile. Cytochrome oxidase activity was determined in brain, kidney and liver homogenates two hours after acrylonitrile was administered intraperitoneally in rats (100 mg/kg). *In vitro* determinations were made in a Warburg flask. Acrylonitrile did not cause changes in the spectrum of cytochrome oxidase.

3) Effect of Cyanide Antidotes

Dudley and Neal (1942) tested whether administration of sodium nitrite, a protective agent in cyanide poisoning, would also act as a protective agent for acrylonitrile. Dogs, rabbits, and guinea pigs were injected with sodium nitrite immediately before or after exposure to acrylonitrile vapors. For rats and rabbits, sodium nitrite injected (i.p. or i.v.) prior to exposure delayed the onset, and reduced the severity of signs, while injection after exposure often prevented death and hastened recovery. Injection (i.p.) of sodium nitrite was of no value in guinea pigs. Ghiringhelli (1954) confirmed that anticyanide agents (sodium thiosulfate and nitrite) were ineffectual for guinea pigs. Dudley and Neal (1942) suggested that dogs and rabbits metabolize acrylonitrile to hydrogen cyanide but guinea pigs may metabolize it in a different manner or detoxify cyanide efficiently and rapidly.

Benes and Cerna (1959) administered cyanide antidotes (sodium nitrite or sodium thiosulfate) to Wistar rats or H strain mice intoxicated with acrylonitrile. Mice tolerated three times the LD_{50} of acrylonitrile when given a combination of the antidotes, and 30% of the rats survived the LD_{100}. Benes and Cerna (1959) suggest that acrylonitrile is toxic to mice by the development of cyanide, but that in rats, the toxicity is not exclusively due to formation of this anion.

Inbred male white mice were given hydroxycobalamin and sodium thiosulfate (both cyanide antidotes) with acrylonitrile (Graham, 1965). Tolerance for acrylonitrile was markedly decreased, as these increased lethal dose values show (LD_{50} values were determined at 2 and 24 hours):

	LD_{50} (mg/kg)[a]	
	At 2 hr	At 24 hr
AN (s.c.) alone	50	25
Hydroxycobalamin[b] and AN	110	85
Hydroxycobalamin[b], AN, and Sodium thiosulfate[c]	250	120
Sodium thiosulfate[d]	>2500	>2500

[a] 60-70 male inbred mice used in each of the 4 groups

[b] 100 mg/kg i.p.

[c] 400 mg/kg, as a solvent for hydroxycolbamin

[d] dose not specified

Graham (1965) attributed the immediate lethal effect of acrylonitrile in mice to cyanide liberation and the delayed effect to a direct effect of acrylonitrile upon the central nervous system.

Experiments using cyanide antidotes show apparent species differences regarding the importance of cyanide liberated from acrylonitrile. McLaughlin et al. (1976) confirmed variations in species susceptibility by comparing the effect of 3 antidotes in mice, rats, rabbits and dogs (Table 46).

b. Direct Action of Acrylonitrile

Paulet et al. (1966), as a result of their studies on mice, rats and rabbits, proposed that there were direct toxic effects of acrylonitrile and that cyanide is not involved to any degree. The following factors were cited in support of their conclusions:

Table 46

Mortality (%) in Several Species after Administration of a Lethal Dose of Acrylonitrile (LD_{100}) and an Antidote (McLaughlin et al., 1976)[a]

Antidote	mice	rats	rabbits	dogs
cysteine hydrochloride	30	10	0	0
sodium thiosulfate	100	20	50	100
sodium nitrite and sodium thiosulfate	100	80	17	100

[a] meeting abstract; number of animals used not specified

i) the signs caused by CN^- and AN are different (AN produces a nervous reaction while CN^- causes anoxia);

ii) AN depresses respiration while CN^- stimulates respiration;[a]

iii) AN initially stimulates oxygen consumption which is not seen in CN^- intoxication;

iv) AN causes hyperglycemia and lowers inorganic P in the blood while in CN^- poisoning there is normoglycemia and elevated inorganic P.

Other authors claim some involvement of cyanide in addition to direct participation of acrylonitrile or its other metabolites (Gut et al., 1975; Hashimoto and Kanai, 1965).

C. Nonmammalian Vertebrates

Data are available for several species of bony fish. Acute and subacute bioassays, as well as the effect of acrylonitrile on fish flavor, are presented below. No information was found on the toxicity of acrylonitrile to nonaquatic nonmammalian vertebrates.

---

[a] however,CN- also depressed respiration as a secondary effect

1. Acute Toxicity

The acute toxicity of acrylonitrile has been described for several species of freshwater and marine fish.

a. Freshwater Fish

Henderson et al. (1961) determined the toxicity of acrylonitrile in fathead minnows *(Pimephales promelas)*, bluegills *(Lempomis macrochirus)* and guppies *(Lebistes reticulatus)*. Acute toxicity was determined by a static bioassay at 25°C. Ten fish per species were added to each of 5 AN concentrations (1.0, 1.8, 3.2, 5.6 or 10 mg/l). Twenty-four, 48 and 96 hour TL_m* values were computed by graphical interpolation and appear in Table 47.

TL_m values ranged from 25.5 to 44.6 mg/l at 24 hours and from 11.8 to 33.5 mg/l at 96 hours. Longer exposure time, therefore, increased toxicity. This exposure effect was not as marked or was nonexistent for other organic nitriles tested: lactonitrile, benzonitrile, acetonitrile, adiponitrile, and oxydipropionitrile. For fathead minnows results of tests in hard or soft water were not appreciably different (Table 47). Bluegills were most, and guppies were least sensitive to acrylonitrile.

Goldfish *(Carassius* sp.) may be somewhat more resistant than guppies. The LC_{50} after 96 hours is 40 mg/l (Paulet and Vidal, 1975).

White crappie *(Pomoxis annularis)* exposed, in a constant-flow constant-concentration system, to 18 and 24 ppm acrylonitrile, died after 180 and 500 minutes, respectively (Renn 1955). No deaths occurred when exposed to 6 or 10 ppm AN.

Bluegills *(Lepomis machrochirus)* survived 0.1 to 1.0 ppm AN for more than 24 hours when tested in static and continuously flowing

---

*TL_m = median tolerance limit; the concentration of a substance which will kill 50% of the test organisms within a specified time.

Table 47

Median Tolerance Limit Values (TL_m) for Various Fish Exposed to Acrylonitrile

Species	Dilution Water[a]	TL_m (mg/1)			Reference
		24 hr	48 hr	96 hr	
Fathead Minnows[b] *(Pimphales promelas)*	hard	32.7	16.7	14.3	Henderson et al., 1961
Fathead Minnows[b] *(P. promelas)*	soft	34.3	21.5	18.1	Henderson et al., 1961
Minnow *(Phoxinus phoxinus)*	NR	38.2	17.6	-	Marcoci and Ionescu, 1974
Bluegill[c] *(Lepomis macrochirus)*	soft	25.5	14.3	11.8	Henderson et al., 1961
Guppy[d] *(Carassius sp.)*	soft	44.6	33.5	33.5	Henderson et al., 1961
Goldfish *(Carassius sp.)*	NR	-	-	40[e]	Paulet and Vidal, 1975
Carp *(Cyprinus carpio)*	NR	37.4	24.0	-	Marcoci and Ionescu, 1974
Pin Perch[g] *(Lagodon rhomboides)*	NR	24.500	-	-	Daugherty and Garrett, 1951
Rainbow Trout *(Salmo gairdneri)*	hard		70		Jackson et al, 1970

[a] hard water - pH 8.2; alkalinity 320 ppm; acidity o ppm; hardness 380 ppm
soft water - pH 7.4; alkalinity 16 ppm; acidity 2 ppm; hardness 20 ppm

[b] 50.8-63.5 mm/long (2-2.5 inches); weight 1.5 g

[c] 38.1-50.8 mm/long (1.5-2 inches); weight 2 g

[d] 25.4 mm long (1 inch); weight 0.1 g

[e] in text, identified as LC_{50}; fish observed for 3 days

[f] authors reported similar values for the bitterling *(Rhodeus sericeus)* and fry *(Leucaspius delineatus)*

[g] 57-113 mm long

NR = not reported

systems. According to Renn (1955) the tolerable levels of acrylonitrile at 25°C is between 10 and 18 ppm for the 2 species tested.

Bandt (1953) determined the effect of acrylonitrile on 2 species of freshwater fish, the roach (*Alburnus* sp.) (11-16 cm long) and the bleak (*Rutilus* sp.) (13.5-15.5 cm long). Acrylonitrile was introduced into a 6 liter aquarium (pH 7.3-7.5; 12.3-18.2°C) at concentrations of 20 to 100 mg AN/l. In all, 10 roaches and 5 bleaks were tested. Two roaches, one each subjected to 30 or 40 mg AN/l, showed no effect by day 11 or 6, respectively. One tested at 50 mg/l died after 68 hours while others tested at 60-100 mg/l died after 22-29 hours. For bleaks, AN at 20 mg/l was without effect by day 20 but at 25 mg/l one bleak died after 16 days. Forty mg/l was lethal after 47 hours while 50 mg/l was lethal after 20 hours. From these limited data Bandt (1953) suggests fish can tolerate 20-25 mg/l of acrylonitrile discharged in wastewater.

b. Marine Fish

Daugherty and Garrett (1951) determined toxicity levels of acrylonitrile in pin perch, *Lagodon rhomboides*. Groups of eight fish acclimatized in 30 liters of seawater were used in static tests. Acrylonitrile was introduced into the aquarium in a series of 16 dilutions (0.25-60.00 mg/l) and the time to death was recorded. Twenty mg/l was the maximum concentration at which no deaths occurred, 30 mg/l being the minimum lethal concentration. No deaths occurred in control fish. The TL_m at 24 hours, determined by interpolation, was 24.500 mg/l (Table 47).

2. Subacute Toxicity

Subacute flow-through bioassays were performed on fathead minnows by Henderson et al. (1961). In five replicate experiments, fifty fish were exposed to each of 7 concentrations of acrylonitrile for 30 days. Solutions in the aquaria (soft water, at 25°C) were renewed every 100 minutes; fish were fed daily. Mean TL_m values from the 5 replicates appear below:

Exposure (day)	1	2	3	4	5	10	15	20	25	30
TL_m (mg/l)	33.5	14.8	11.1	10.1	8.1	6.9	5.2	4.2	3.5	2.6

According to Henderson et al. these results indicate a continuous cumulative effect. The authors point out that shorter term TL_m studies, therefore, do not adequately indicate acrylonitrile's toxicity.

Jackson et al. (1970) exposed rainbow trout to AN at concentrations between 2 and 200 mg/l. When exposure was at 2.2 mg/l (this is 1/25 of the 48 hr LC_{50}; table 47) fifty percent of the test organisms were dead in 100 days. The authors identified a further hazard: 1 day exposure to "certain concentrations" of acrylonitrile, followed by transfer of the trout to clean water resulted in the deaths of all the fish after 5-10 days.

The first sign of acrylonitrile toxicity in fathead minnows (after at least 10 hours at 50 mg/l) was darkening of the skin (Henderson et al., 1961). At some lower concentrations fish would live for 10-20 days, then darken and die within 1-3 days.

3. Effect on Taste of Fish

Fifteen adult bluegills were exposed to a sublethal concentration of 5.0 mg/l acrylonitrile (in soft water) for 1 to 4 weeks. Six samples of these fish were baked and flavor was evaluated by 14 persons and compared to control fish. There was no objectionable taste to the exposed fish (Henderson et al., 1961).

D. Invertebrates

Limited data are available for aquatic and nonaquatic invertebrates.

1. Aquatic Organism Toxicity

The 24 hour LC_{50} for acrylonitrile in Brown shrimp *(Crangon crangon)* is 10-33 mg/l. Eight to 25 animals were exposed to serial dilutions in 10 gallons of seawater (15°C) for this static bioassay (Portmann and Wilson, 1971).

Bandt (1953) exposed several species of arthropods to 25-100 mg of acrylonitrile per liter of water. The species examined were gammarus (a freshwater shrimplike crustacean) and larvae of 3 types of insects. Dose-related effects were obtained as follows:

AN concentration (mg/l)	Organism	No. Tested	Response
25	caddisfly larvae	2	1 dead at 48 hr
	mayfly larvae	1	dead at 72 hr
	gammarus	10	(no effect by day 3)
50	caddisfly larvae	4	3 dead at 48 hr
	mayfly larvae	3	dead at 48-72 hr
	dragonfly larvae	1	(no effect by day 4)
	gammarus		9 dead at 22 hr; 1 dead at 46 hr
100	gammarus	10	dead at 22-48 hr
	caddisfly larvae	1	(no effect by 72 hr)

2. Nonaquatic Organism Toxicity

Bond and Buckland (1976) determined lethal dose values of acrylonitrile-methyl bromide mixtures to three species of insects. About 300 granary weevils *(Sitophilus granarius)* 300 flour beetles *(Tribolium confusum)* and 90 cadelle larvae *(Tenebroides mauritanicus)* were exposed in each of 5 or 6 concentrations in each of 7 tests. Exposure was for 8 hours in a 525 liter fumigation chamber. Lindgren et al. (1954) exposed 8 species of insects for 2 and 6 hours. LD_{50} and LD_{90} values for acrylonitrile appear in Table 48. Acrylonitrile alone was more effective at controlling insects than methyl bromide alone or mixtures of acrylonitrile and methyl bromide. However, acrylonitrile is not used alone as a fumigant because it is flammable; methyl bromide is nonflammable (Bond and Buckland, 1976)

Fruit flies *(Drosophila melanogaster)* showed no increase in mutation rates when exposed to acrylonitrile (refer to Section IV-A-2 for details).

E. Plants

Acrylonitrile was one of about 35 compounds tested for biological activity in pea seedlings *(Pisum sativum)* (Burg and Burg, 1967). Specifically, acrylonitrile was inactive in the pea Straight Growth Test, one which determines elongation using Michaelis-Menten kinetics. Concentrations of 0.17 mM acrylonitrile were "toxic" (undefined by authors) to seedlings; lower levels did not affect elongation.

Acrylonitrile-carbon tetrachloride (50 AN:50 CCl_4) fumigant mixtures were tested for adverse effects on seed germination under laboratory conditions (Glass and Crosier, 1949). Fumigation with AN-CCl_4 at concentrations

Table 48

Lethal Dose Values of Insects Exposed to Acrylonitrile[a]

Species	LD_{50} (mg/l)	Length of Exposure (hr)	LD_{90} (mg/l)	Length of Exposure (hr)	Reference
Granary Weevil	0.7	8	1.2	8	Bond and Buckland, 1976
Sitophilus granarius	2.0	6	2.9	6	Lindgren et al., 1954
	4.5	2	8.0	2	Lindgren et al., 1954
Rice Weevil	1.0	6	1.8	6	Lindgren et al., 1954
Sitophilus oryza	2.5	2	6.5	2	Lindgren et al., 1954
Mexican Bean Weevil	1.4	6	2.1	6	Lindgren et al., 1954
Zabrotes pectoralis	2.0	2	4.0	2	Lindgren et al., 1954
Drug-store Beetle	1.7	6	2.5	6	Lindgren et al., 1954
Stegobium paniceum	3.0	2	7.0	2	Lindgren et al., 1954
Flour Beetle	1.9	8	2.5	8	Bond and Buckland, 1976
Tribolium confusum	3.0	6	4.9	6	Lindgren et al., 1954
	6.5	2	11.0	2	Lindgren et al., 1954
Bean Weevil	1.1	6	2.0	6	Lindgren et al., 1954
Acanthoscelides obtectus	3.0	8	5.5	8	Lindgren et al., 1954
Saw-Toothed Grain Beetle	0.8	6	1.4	6	Lindgren et al., 1954
Oryzaephilus surinamensis	3.5	2	6.5	2	Lindgren et al., 1954
Lesser Grain Borer	0.8	6	2.5	6	Lindgren et al., 1954
Rhyzopertha dominica	1.4	2	4.0	2	Lindgren et al., 1954
Cadelle *Tenebroides mauritanicus*	2.8	8	6.0	8	Bond and Buckland, 1976

[a] adults tested for all species with the exception of the Cadelle (4th instar)

ranging from 1 to 25 pounds per 1000 cubic feet for 24 to 48 hours had no effect on germination in any of the seeds tested, which included beans, beets, corn, lettuce, peas, onions, tomatoes, wheat, and oats.

Acrylonitrile is "highly toxic" to nursery stock and growing plants and "damages" fresh fruit (WHO, 1965). No other information is given in this source.

F. Microorganisms

1. Microorganisms Used in Mutagenicity Tests

Acrylonitrile was mutagenic in bacteria and yeast under some experimental conditions, but not others, as discussed in Section IV-A-3. As part of mutagenicity testing, some investigators reported toxic levels. Acrylonitrile was slightly toxic at 100 ul/plate while "essentially complete killing" occurred at 500 ul/plate for 5 strains of *Salmonella typhimurium* and 1 strain of *Saccharomyces cerevisiae* (Litton Bionetics, Inc., 1975). Concentrations of 500 to 10,000 μg/plate were not toxic to three stains of *S. typhimurium* (Haskell Laboratory, 1975). Venitt et al. (1977) reported increasing toxicity to several *E. coli* strains at concentrations above 150 μmol/plate.

Loveless et al. (1954) screened acrylonitrile for effects on growth and division in yeast, *Saccharomyces cerevisiae*, and in bacteria, *Escherichia coli* strain B. Culture dry weights and direct cell counts were determined to measure growth and division, respectively, during the logarithmic phase of growth. Average cell weights (total mass/number of cells) were taken as another measure of effects on division. An increase in the weight of treated cells compared to controls shows interference with division. Acrylonitrile at 1000 ug/ml reduced the growth of *E. coli* by about 50% but had no effect on cell size. However, at this concentration, both growth and division were reduced in *S. cerevisiae*. In yeast, treated cells weighed 52% of controls and were 170% the size of controls.

Acrylonitrile supported growth of *Nocardia rhodochrous* (LL 100-21) as a source of nitrogen, but not of carbon (DiGeronimo and Antoine, 1976). Cells were inoculated into culture tubes containing 10 mg AN/ml in broth.

2. Molds on Food

Acrylonitrile effectively controlled mold growth on papads, an Indian bread (Narasimhan, et al., 1972). Papads are often infested with mold at about 18% moisture. Packages of 16 insect-infested papads (at 18 and 20% moisture) were fumigated with 32 or 64 mg AN/l. After one month, no mold growth was observed at the higher dose at either moisture content; at the lower dose at 18% moisture no effects occurred but moderate mold growth developed in the presence of 20% moisture.

3. Aquatic Microorganisms

Acrylonitrile was added to aerated river water supplemented with nitrogen and phosphorus (Cherry et al., 1956). When 10 or 25 mg/l AN was used, a balanced biota developed, including bacteria, diatoms, algae, protozoa, and rotifers. However, at 50 mg/l, diversity was decreased and growth was predominantly fungal. The authors suggest acrylonitrile at 50 mg/l is undesirable in a stream.

The tolerance of river microorganisms to acrylonitrile was discussed in Section II-E-1 in relation to biological oxidation.

G. *In Vitro* Studies

1. Effect on Isolated Nerves

Sciatic-gastrocnemius preparations were isolated from frogs *(Rana nigro maculata)* and tested for conductivity after the addition of acrylonitrile and other materials in physiological saline (Hashimoto and Kanai, 1965). Measurements were made of the time required for anesthesia and the duration of anesthesia. The anesthetic effect of AN was similar to that of local anesthetics (novocaine and ethyl alcohol) and general narcotics (ethyl ether and urethane). The authors suggest the anesthetic effect of AN *in vitro* was stronger than that estimated to be possible *in vivo*.

2. Effect on Tissue Respiration

Brain cortex slices were prepared from male guinea pigs and measured for oxygen consumption using untreated and K^+-stimulated tissues (Hashimoto and Kanai, 1965). At concentrations of 10^{-3}M acrylonitrile (a toxic concentration *in vivo*), there was a 20% inhibition of K^+-stimulated respiration but no effect on unstimulated respiration. The inhibitory effect of AN was unaffected when sodium thiosulfate (a cyanide antidote) was added with acrylonitrile. Sodium cyanide inhibited both stimulated and unstimulated respiration but the inhibitory effect was counteracted by sodium thiosulfate. These results suggest the effect of acrylonitrile on the brain might be due to the acrylonitrile molecule *per se* rather than its metabolite cyanide.

The oxygen consumption of guinea pig liver slices was measured at concentrations of 10^{-3} M AN and 5×10^{-2} M AN (Hashimoto and Kanai, 1965).

There was no inhibition of oxygen consumption at the lower concentration, which is toxic *in vivo* (as just discussed, brain slice respiration was inhibited at this concentration). At the higher level, there was an inhibitory effect on liver slices, probably due to protein denaturation. Hashimoto and Kanai (1965) suggest that acrylonitrile has little effect on organs other than the nervous system. At high concentrations, however, the compound also affects liver function, possibly by changing the structure of proteins.

3. Effect on Tissue Sulfhydryl Content

Acrylonitrile resulted in decreased sulfhydryl content of *in vitro* preparations of blood, liver, and kidney slices from guinea pigs (Hashimoto and Kanai (1972), as previously discussed (refer to Table 38).

IV. SPECIAL EFFECTS

A. Mutagenicity

1. Broad Bean, *Vicia faba*

Acrylonitrile was not mutagenic (radiomimetic) in *Vicia faba* (Loveless, 1951). Root tips exposed to acrylonitrile for 1 hour at several unspecified concentrations were unaffected in regard to either dividing cells (examined 4-6 hours after treatment) or resting cells (examined 18, 36, or 48 hours after treatment).

Acrylonitrile was also without mutagenic action in *Vicia faba* when tested by the light-acridine orange system (Kihlman, 1961). Root tips were pretreated with acridine orange (functions to absorb light energy) then exposed to light for 30 minutes. The roots were simultaneously exposed to a maximum of 1000 μM acrylonitrile (15 minutes before illumination and during illumination). Twenty-six hours after treatment the root tips were fixed and metaphase cells examined. Acrylonitrile had not produced structural chromosomal changes.

2. Fruit Fly, *Drosophila melanogaster*

Benes and Sram (1969) screened acrylonitrile for mutagenic activity in *Drosophila melanogaster* using the Muller-5 genetic test. This test detects recessive lethality in the X-chromosome. Acrylonitrile (0.1%) was injected into the abdomen. Frequency of mutations were 0.35% (2 recessive lethals out of 572) for postmeiotic germ stages and 0.55% (4 out of 725) for premeiotic and meiotic stages. These rates are not considered different from spontaneous mutation rates (0.14%) by the authors.

3. Bacterial Systems

a. Ames Standard Plate Method

Several laboratories have evaluated the mutagenic activity of acrylonitrile in *Salmonella typhimurium* using the Ames standard plate method. Most or all of the following histidine auxotrophs (*his*) *Salmonella* strains were used: a) TA 1535, sensitive to base-pair substitution mutagens; b) TA 1537 and TA 1538, sensitive to frameshift mutagens; c) TA 98 and TA 100 (derived from TA 1538 and TA 1535, respectively, by the introduction of the R factor plasmid pKM101). The latter strains may be more sensitive to some mutagens. The testing procedure includes mixing the indicator organism with the test chemical, pouring the mixture onto minimal agar plates then counting the number of his^+ revertants after an incubation period. In a similar manner, tests are also made by mixing the indicator organism and a metabolic activation system (here, rat liver homogenate) with the test chemical (SRI, 1976). These tests have been carried out for acrylonitrile at the 3 laboratories described below.

Haskell Laboratory (1975; DuPont). Three *S. typhimurium* strains were used (TA 1537, TA 1538, TA 1535) with and without metabolic activation. Concentrations of acrylonitrile ranged from 500 to 10,000 μg per plate (0.62-12.4 μl)*. Weak but reproducible mutagenic activity was observed in strain TA 1535 with metabolic activation between 500-1500 μg AN/plate (1.62-1.86 μl). A 4-5 fold increase in the mutation frequency or the spontaneous frequency was observed in 5 replicate trials. Inconclusive results were obtained with non-activated strain TA 1535. In one out of 5 non-activated trials, there was positive mutagenic activity at 2500 μg AN/plate (3.1 μl).

*conversion 806 μg = 1 μl

Litton Bionetics (1975). Five strains of *S. typhimurium* (TA 1535, TA 1537, TA 1538, TA 98, TA 100) were tested with and without metabolic activation at 0.1-100 μl AN/plate. No mutagenic activity was observed.

Stanford Research Institute (1976). Five strains of *S. typhimurium* (TA 1535, TA 1537, TA 1538, TA 98, TA 100) were tested with and without metabolic activation at 0.1-5000 μg AN/plate (.0001-6.2 μl). No mutagenic activity was found. TA 100 was retested at 1000-4000 μg AN/plate and again there was no mutagenic effect.

b. Modified Ames Method

Milvy and Wolff (1977) tested three strains of *S. typhimurium:* TA 1535, sensitive to base-pair substitutions; TA 1978 and TA 1538, sensitive to frameshift mutagens. Three methods of exposure were used: spotting acrylonitrile and liver homogenate on a "lawn" of *Salmonella;* shaking acrylonitrile, liver homogenate and bacteria; exposing liver homogenate and bacteria to acrylonitrile vapors. Low level mutagenic activity was indicated in strain TA 1535 at 5 or 10 μl AN utilizing the first method and in TA 1535 strains employing the second. Data are not presented for tests in the absence of microsomes and/or co-factors but the authors stated no mutagenesis occurred under those conditions.

Milvy and Wolff (1977) pointed out that the ease with which acrylonitrile vaporizes makes uncertain the actual amount of acrylonitrile in the test system. They found the third method (vapor exposure) to be more quantitative. Strain TA 1535 was exposed to acrylonitrile vapor at concentrations ranging from 2-200 μl for 0.5 to 4 hours; strain TA 1538 was exposed for 2 hours at 200 μl AN. As shown in Table 49, the number of revertants was increased for every acrylonitrile exposure condition.

Table 49

Mutagenicity of Acrylonitrile Vapor With *S. tyhimurium* Strain TA 1535 (Milvy and Wolff, 1977)

Method of exposure	Time of exposure (h)	Acrylonitrile (μl)	Revertants (per ml)	Viable cells per ml (10^{-8})	Revertants per 10^8 viable cel
Vapor	0.5	200	195(6)[a]	3.8(2)[a]	51
		0	111(6)	4.7(2)	24
	1.1	300	1770(3)	3.2(2)	553
		0	350	13.0(2)	26
		200	100(2)	4.5	22
		0	45(2)	2.7	12
		100	250	4.2	60
		0	110	4.4	25
		25	105(2)	2.7	39
		0	60	2.0	30
	1.5	250	157(4)	1.6	98
		0	33(2)	2.2	15
	2	200	369(12)	3.8(12)	97
		0	79(12)	4.7(12)	16.8
		100	220(6)	1.8	12
		0	140(6)	1.7	8.2
		5	250(4)	8.6(2)	29
		0	67(4)	6.1(2)	11
	3	5	580(6)	3.8(4)	153
		0	162(6)	4.1(4)	40
	4	2 (57 ppm)	383(6)	11.5(2)	33
		0	207(6)	12.5(2)	17

---

[a] The first number is the number of colonies per plate, averaged over the number of plates exposed which is shown in parenthesis. When no parenthetical number is shown, only a single plate was exposed.

c. Mutagenicity in *Escherichia coli*

Venitt et al. (1977) tested the mutagenicity in *E. coli* WP2 series bacteria. Strains in this series have an ochre mutation in the *trp*E locus of the tryptophan-synthetase operon. Mutants are scored as revertants to tryptophan independence ($trp^- \rightarrow trp^+$). These strains were tested: WP2 (DNA - repair proficient); WP2 *uvr*A (lacks excision repair); WP2 *uvr*Apc/A (lacks both excision repair and DNA-polymerase); WP2 *lex*A (deficient in an error-prone pathway).

In one series of experiments mutagenicity was assayed by a plate-incorporation method. Strains were mixed with graded doses of acrylonitrile; plates were scored for revertant colonies after three days. Mutagenic effects in 3 strains (WP2, WP2 *uvr*A; WP2 *uvr*Apo/A) was weak but reproducible and statistically significant (analysis of variance). Strain WP2 *lex*A was not reverted by acrylonitrile; marked toxicity might have been a factor. Addition of a metabolic activation system had no effect on the mutagenic action of acrylonitrile so the authors concluded the compound to be a directly acting mutagen.

In a second series of experiments, the simplified fluctuation test of Green et al. (1976) was used. This test confirmed the mutagenicity of acrylonitrile at levels as low as 0.1×10^{-3} M.

Further confirmation of acrylonitrile's mutagenic effect was obtained from tests of *E. coli* WP2 containing the resistance-transfer factor pkM101. Introduction of this plasmid enhanced the mutagenic effects of acrylonitrile.

Venitt et al. (1977) suggest that acrylonitrile acts by causing non-excisable mis-repair DNA damage associated with the generation of DNA strand breaks; this is based on the differential response of the tester strains. The authors hypothesize that acrylonitrile might react with thymine residues in DNA.

4. Yeast, *Saccharomyces cerevisiae*

Litton Bionetics, Inc. (1975) evaluated the ability of acrylonitrile to induce mutations in strain D4 yeast. Assays were conducted with and without metabolic activation preparations (rat liver microsome) at 0.1, 1, 10, or 100 µl AN/plate. The number of revertants per plate were counted. In nonactivation tests, 10 and 100 µl AN/plate indicated possible mutagenic activity (54% and 64% more revertants/plate, respectively than solvent controls). Activation tests with D4 were negative.

5. Mammalian *in vitro* Assays

Acrylonitrile was evaluated for specific locus forward mutation induction in the L5178Y thymidine kinase mouse lymphoma cell assay (Litton Bionetics, Inc., 1976). No mutagenic activity was found.

The lymphoma cells are heterozygous for a particular autosomal mutation at the TK locus and are bromodeoxyuridine (BUdR) sensitive. Cells were tested in the presence and absence of a rat liver microsomal system. The assay will detect forward mutation to TK-/-cells that are resistant to BUdR. The procedure of Clive and Spector (1975) was used. Concentrations of 0.01-0.0005% AN were tested (initial tests showed levels of 0.05 and 0.1% AN were toxic to the test system). As shown in Table 50, mutation frequencies were increased at the higher concentrations compared to control. Litton Bionetics, Inc. (1976) suggest that these increased mutation frequencies were the result of high toxicity, rather than the induction of mutations.

6. DNA Repair Assay

Litton Bionetics (1976) reported that acrylonitrile is negative at 10 µl/plate with or without an activation system when tested in the DNA repair assay (Slater et al., 1971).

According to OSHA the variation of test results discussed above appears to be "closely related to the differences in the laboratory methods used and to the high volatility and toxicity of AN...these studies could not be said to show that AN is non-mutagenic." (Bingham, 1978). Mike Prival, a microbiologist at the FDA, evaluated the mutagenicity studies and suggested the discrepancy in results might be due to the following: i) samples and purity of the AN used may have been quite different; ii) minor differences in assay techniques might have facilitated or prevented the evaporation of AN. He suggests further testing but cautions that unnecessary human exposure be prevented until the issue of its carcinogenic potential is resolved (Prival, 1977).

B. Cytogenicity

No chromatid or chromosomal aberrations were detected in 16 male Sprague-Dawley rats (Spartan substrain, SPF-derived) exposed for 90 days to 0, 35, 210, or 500 ppm of acrylonitrile (Johnston et al., n.d.). Bone marrow cells were scored for aberrations; 25 to 50 metaphase spreads were scored per animal. No abnormalities were found.

C. Teratogenicity

Murray et al. (1976; MCA sponsored) reported adverse maternal and fetal effects after pregnant rats were given oral doses of 25 or 65 mg AN/kg/day during gestation. Groups of 29-39 pregnant Sprague-Dawley rats (265 g) were given 10, 25 or 65 mg AN/kg by gavage on days 6-15 of gesta-

Table 50

Testing of Acrylonitrile in the Mouse Lymphoma
LS178Y Assay (Litton Bionetics, Inc., 1977)

		Mutation Frequency x 10^6[a]	
	Dosage %	Nonactivation	Activation (mouse liver)
Negative Control[b]		11.8	14.5
Positive Control[c]		223.0	257.0
AN	0.01	23.5	21.5
	0.005	13.3	11.4
	0.001	9.8	10.3
	0.0005	7.0	4.5
Negative Control[b]		0.1	14.2
Positive Control[c]		196.0	272.7
AN	0.03	10.2	34.2

[a] computed by dividing the numbers of clones formed in BUdR-selection medi by number found in medium without BUdR

[b] solvent in which test compound was dissolved

[c] dosage 0.1% ethylmethanesulfonate (EMSF) for nonactivation tests
dosage 1.0% dimethylnitrosamine (DMNA) for activation tests

tion. Forty-three controls received 2 ml/kg of water alone. Rats were sacrificed on day 21 of gestation.

Maternal Effects. Maternal effects were clearly dose-related. For rats receiving the highest dose (65 mg AN/kg) significant changes were noted compared to control: decreased weight gain; increased liver weight (both relative and absolute); decreased food intake on days 6-8 of gestation only; increased water consumption throughout days 6-20 of gestation; fewer visible implantation sites.

For rats receiving 25 mg AN/kg the only adverse effect was a significantly lowered food intake on days 6 to 8 of gestation. Rats receiving 10 mg AN/kg were unaffected. At all doses there was no significant effect on litter size, fetal sex ratio, or the incidence or distribution of resorptions.

Fetal Effects. External, soft tissue and skeletal examination revealed significant dose-related effects (Table 51).

65 mg/kg - lower fetal body weight, lower crown-rump length; increased frequency of acaudate fetuses; increased frequency of missing vertebrae (other than a single thoracic and single lumbar vertebra);increased incidence of fetuses missing more than one pair of ribs; delayed ossification of the 5th sternebrae; split 2nd sternebrae; missing centra of cervical vertebrae.

25 mg/kg - The incidence of either soft tissue or skeletal alterations was not significantly different from control although some of the same malformations were observed at the higher dose (Table 51).

10 mg/kg - no adverse effects noted.

Table 51

Incidence of Fetal Alterations Observed During the External, Soft Tissue or Skeletal Examination Among Litters of Rats Receiving Acrylonitrile by Gavage (Murray et al., 1976)

		Dose Level of Acrylonitrile, mg/kg/day[a]			
		0	10	25	65
		No. Fetuses Examined			
EXTERNAL EXAMINATION		443	388	312	212
SOFT TISSUE EXAMINATION		154	135	111	71
SKELETAL EXAMINATION		443	388	312	212
SKULL BONE FORMATION		289	253	201	141
EXTERNAL EXAMINATION		% Affected (No. Affected)			
Acaudate	F[b]	0	0	0.6(2)	2(4)[c]
Acaudate or short tail	F	0.2(1)	0	0.6(2)	4(8)[c]
Short trunk	F	0	0	0	1(3)[c,d]
Imperforate anus	F	0	0	0	1(2)[d]
SOFT TISSUE EXAMINATION					
Right-sided aortic arch	F	0	0	1(1)	1(1)[d]
Ovaries, anteriorly displaced	F	0	0	1(1)[d]	1(1)[d]
Missing kidney, unilateral	F	1(1)	0	0	1(1)[d]
Dilated renal pelvis, unilateral	F	0	0	2(2)	0
Dilated ureter, left	F	0	0	1(1)	1(1)[d]
SKELETAL EXAMINATION		% Affected (No. Affected)			
Vertebrae - 12 thoracic & 5 lumbar (normal # is 13 T and 6 L)	F	2(7)	0	2(7)	0
- missing vertebrae other than 1 thoracic lumbar[c]	F	0.2(1)[d]	0	0.6(2)[d]	4(8)[c,d]
-missing centra of cervical vertebrae (other than C_1 and C_2)	F	5(23)	8(30)	10(31)	34(71)[c]
Ribs					
-missing 13th pair only	F	2(7)	0	2(7)	0
-missing more than 1 pair	F	0	0	1(2)[d]	2(4)[c,e]
Sternebrae					
-delayed ossification, 5th	F	2(9)	3(13)	4(13)	15(31)[c]
-missing, 5th	F	0	0	1(2)	1(2)
-split, 5th	F	1(4)	1(3)	1(3)	4(8)
-split, 2nd	F	0	0	0	2(4)[c]

Table 51 (cont'd)

Incidence of Fetal Alterations Observed During the External, Soft Tissue or Skeletal Examination Among Litters of Rats Receiving Acrylonitrile by Gavage (Murray et al., 1976)

		Dose Level of Acrylonitrile, mg/kg/day[a]			
		0	10	25	65
		% Affected (No. Affected)			
SKULL BONE EXAMINATION					
-delayed ossification any skull bone	F	7(21)	6(15)	6(12)	4(5)

---

[a] Acrylonitrile was given by gavage on days 6-15 of gestation; additional data and incidence of alterations in litters given in reference

[b] F = fetuses

[c] Significantly different from control by a modified Wilcoxon test, $p < 0.05$

[d] This alteration occurred only in fetuses with a short or missing tail at this dose level.

The authors suggest the malformations are not the effect of maternal toxicity alone, implying acrylonitrile was somehow acting directly on the embryo or fetus.

Some animals in both the experimental and control groups developed sialodacryodenitis (rat mumps). As shown in Table 51, some control rats also developed gross terata, but at a lower level. T. Collins, a pharmacologist at the FDA, suggests the possibility that there may have been an interaction between the viral infection and the chemical stress which may have caused some of the terata at the 2 highest dose levels. He concludes, however, that acrylonitrile was frankly (i.e., structurally, visibly) teratogenic at the two highest levels administered (Collins, 1977).

Scheufler (1976) described acrylonitrile as embryotoxic to pregnant mice (AB Jena-Halle, C57Bl, and DBA). Acrylonitrile was administered intraperitoneally at several unspecified doses. About 200-300 mice were tested for acrylonitrile and each of several other compounds.

Svirbely and Floyd (1961) carried out reproduction studies in rats. They reported their findings only briefly in a meeting paper. Sprague-Dawley rats given 500 ppm in the drinking water showed decreased fertility, gestation and viability. At this dose, females also developed a progressive muscular weakness in the hind limbs about 16 to 19 weeks after the weaning of the second litter.

D. Carcinogenicity

Recent data have implicated acrylonitrile as a carcinogen. Preliminary results of an epidemiological study at an E. I. DuPont de Nemours and Company textile plant (Camden, S.C.) revealed more than twice the expected incidence of cancer among workers exposed to acrylonitrile as discussed in detail previously (Section III-A-2-d; O'Berg, 1977).

Preliminary findings of long-term inhalation and feeding studies, sponsored by the Manufacturing Chemists Association, indicate an increase of tumors in rats exposed to acrylonitrile. Rats consuming 100 or 300 ppm (mg/l) AN in the drinking water for 1 year developed tumors of the stomach, central nervous system (CNS), and Zymbal gland of the ear canal (Quast et al., 1977). Some rats receiving 35 mg/l developed CNS tumors (Clark, 1977). In rats exposed to an atmosphere containing 80 ppm AN for 6 hours/day for 5 days/week for 2 years there was an increase in the incidence of tumors of the gastrointestinal tract, ear canal, mammary region and brain. Exposure to 20 ppm resulted in an increase in subcutaneous masses of the mammary region and in brain tumors (Clark, 1978). These studies are discussed in more detail elsewhere (III-B-3-c). A final report on the two-year drinking water study is expected by May, 1978. Although interim or preliminary data are not usually considered appropriate for a carcinogenic evaluation "immediate concern" is warranted, particularly because the brain and stomach tumors do not occur spontaneously at the rates observed (Squire, 1978).

Maltoni et al. (1977) conducted carcinogenicity bioassays on Sprague-Dawley rats (initially 12 weeks old) ingesting or inhaling AN for 2 years. All animals were kept under observation until spontaneous death. The authors concluded AN showed a "border-line oncogenic effect."

For the ingestion experiments, AN was administered in olive oil by gavage at a dose of 5 mg/kg body weight, 3 times per week for 52 weeks. Controls received olive oil alone. For the inhalation experiments, rats were exposed to 40, 20, 10, or 5 ppm AN (86.8, 43.4, 21.7 or 10.8 mg/m^3)

for 4 hours/day, 5 days per week for 52 weeks. The number and type of tumors after 131 weeks (end of experiment) for both the ingestion and inhalation experiments appear in Table 52.

The most frequent types of tumors were: i) mammary tumors - moderate increase in both experimental and controls; no clear-cut dose-response relationship; ii) Zymbal gland carcinomas - incidence in treated rats not considered significant; iii) Forestomach papillomas and acanthomas - "moderate increase" under both experimental conditions compared to controls; iv) Encephalic tumors - found in both treated groups and ingestion (olive oil) controls. The authors point out that of 3 tumors observed in animals exposed by inhalation, these occurred at the 2 highest doses of AN. They also stress that the incidence of tumors in the olive oil controls was "surprisingly high"; v) Skin carcinomas - a few observed among rats treated by inhalation; vi) Uterine carcinomas - no significant differences between treated and control rats.

Maltoni et al. (1977) state that these results indicate a "border-line oncogenic effect" and stress the need for further research.

Szabo et al. (1977) found elevated hepatic glutathione levels in rats ingesting acrylonitrile for 21 days. They pointed out that similar increases in glutathione have been described previously for chemical carcinogens, but caution that it is unknown whether such changes correlate with carcinogenicity.

Milvy and Wolff (1977) found acrylonitrile to be mutagenic in the Ames test (see Section IV-A-3) and suggest the need for careful carcinogenic testing.

Table 52

Carcinogenicity Bioassays on Rats
Maltoni et al. (1977); Results After 131 Weeks

A. Ingestion of 5 mg AN/kg, 3 times/week for 52 weeks

	Treated		Control	
	Female	Male	Female	Male
Total N[a]	40	40	75	74
Mammary Tumors (%)	52.5	5.0	44.0	2.7
x̄ Tumors/rat	1.4	1.0	1.4	1.0
Fibroadenomas and fibromas(%)	18	2	26	2
Carcinomas (%)	5.0	-	5.3	-
Fibroadenomas and carcinomas (%)	2.5	-	4.0	-
Zymbal Gland Carcinomas (%)	-	2.5	1.3	-
Forestomach Papillomas and Acanthomas (%)	10.0	2.5	1.3	-
Encephalic Tumors (%)	2.5	-	5.3	1.4
Others (%)	12.5	10.0	12.0	6.7

B. Inhalation in air at 40, 20, 10, 5 ppm (86.8, 43.4, 21.7 and 10.8 mg/m^3) for 4 hr/day, 5 days/week for 52 weeks

	Treated								Control	
Dose (ppm)	40		20		10		5		0	
Sex	F	M	F	M	F	M	F	M	F	M
Total N[a]	30	30	30	30	30	30	30	30	30	30
Mammary Tumors (%)	23.3	13.3	23.3	13.3	23.3	3.3	33.3	-	16.6	3.3
x̄ Tumors/rat	1.4	1.0	1.0	1.0	1.4	1.0	1.2	-	1.0	1.0
Fibroadenomas and fibromas (%)	16.6	10.0	30.0	6.6	23.3	3.3	20.0	-	13.3	6.6
Carcinomas (%)	6.6	3.3	3.3	6.6	-	-	13.3	-	3.3	3.3
Zymbal Gland Carcinomas (%)	-	-	3.3	-	3.3	3.3	-	-	-	-
Forestomach Papillomas and Acanthomas (%)	-	10.0	3.3	-	6.6	6.6	3.3	3.3	-	-
Encephalic Tumors (%)	-	6.6	-	3.3	-	-	-	-	-	-
Skin Carcinomas (%)	3.3	3.3	3.3	-	3.3	-	13.3	-	-	-
Uterine Carcinomas (%)	3.3	-	6.6	-	3.3	-	10.0	-	3.3	-
Others (%)	-	16.0	13.3	23.3	23.3	23.3	10.0	-	13.3	13.3

[a] corrected number; this represents the no. of rats alive after 28 weeks, when the first tumor was observed. Percentages developing tumors calculated using corrected number.

During 1977, the Environmental Protection Agency's Office of Air Quality Planning and Standards (EPA/OAQPS) officially requested that EPA's Carcinogen Assessment Group (EPA/CAG) do a risk assessment on acrylonitrile (Anon. 1977n).

The National Cancer Institute Carcinogenesis Testing Program recognizes AN as carcinogenic to experimental animals and has no plans to further test the compound as a potential carcinogen (Cueto, 1978).

Monsanto is sponsoring two animal-feeding studies to establish a no-effect level for AN. In one study, rats are being fed AN at 1 and 100 ppm in the drinking water. In the second study, 1,3,10, and 100 ppm AN are being administered by gavage (Anon, 1977p).

V. REGULATIONS AND STANDARDS

A. Federal Regulations

1. Occupational Safety and Health Administration

Prior to January 17, 1978, occupational exposure to acrylonitrile had been limited by the Occupational Safety and Health Administration (OSHA; P.L. 91-596) to an 8-hour time weighted average of 20 ppm (~ 45 mg/m^3) (Table Z-1; 29 CFR 1910.1000). This was the level recommended by the American Conference of Governmental Industrial Hygienists (ACGIH, 1971) on the basis of animal exposure data and by analogy with the 10 ppm threshold limit value (TLV) for hydrogen cyanide. On January 17, 1978 OSHA issued an Emergency Temporary Standard (ETS) which reduced the permissible exposure to 2 ppm, with a ceiling level of 10 ppm for any 15 minute period during the 8-hour day. The standard also includes an action level of 1 ppm as an 8-hour time-weighted average (TWA). A permanent standard will be issued by July, 1978. Three sets of permissible exposure limits are under consideration for the permanent standard: 2 ppm AN as an 8-hr TWA; with a 10 ppm ceiling limit over any 15 min period; 1 ppm TWA with a 5 ppm ceiling; and a 0.2 ppm TWA with a 1 ppm ceiling limit. Enviro Control (1978) conducted an economic assessment of these proposed levels. A public hearing on the proposed standard began on March 21, 1978. The proposed levels represent concentrations achievable by engineering controls. There is no implication that these levels are necessarily safe for worker exposure.

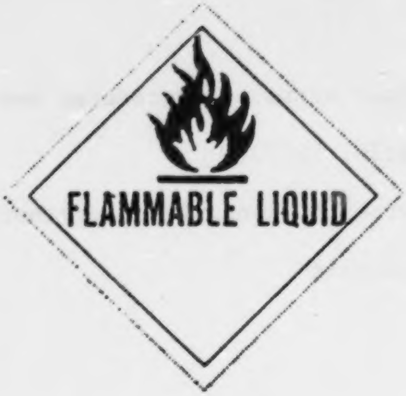
As background to the issuance of the Emergency Temporary Standard, this course of events occurred: On June 29, 1977 OSHA issued a notice requesting information on acrylonitrile stating that the current regulation for worker exposure may not be sufficiently protective and that the issuance of an Emergency Temporary Standard was being considered (42 FR 33043). Such action was based on information recently released from the Manufacturing Chemists Association (interim report on long-term feeding and inhalation studies; teratogenicity study) and DuPont (epidemiology study indicating cancer risks). Based on these and other studies, the National Institute for Occupational Safety and Health (NIOSH) called for handling acrylonitrile in the workplace as if it were a human carcinogen (Finklea, 1977). On September 29, 1977 NIOSH recommended in a Criteria Document sent to OSHA that workplace exposure to acrylonitrile be limited to 4 ppm of air or 8.7 mg/m^3 as determined by a 4-hour sample collected at 0.2 l/min (see section on Detection Methods).

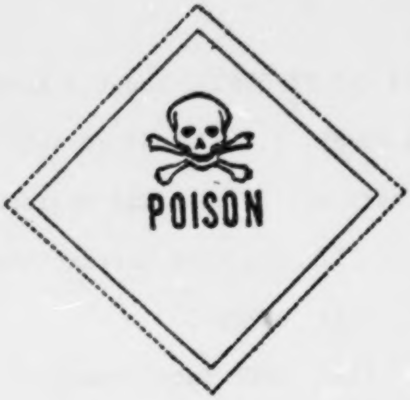
The Emergency Temporary Standard of 2 ppm issued by OSHA was particularly in response to the carcinogenic potential of acrylonitrile. The standard applies to workers engaged in the manufacture of acrylic and modacrylic fibers, ABS and SAN plastics and resins, nitrile rubber, specialty polymers, plastic and polyurethane intermediates, and polymer solutions. Related activities such as packaging, repackaging, storage, transportation and disposal of acrylonitrile are also covered. Many processes where acrylonitrile is present in only small amounts are excluded from the standard.

2. Department of Transportation

Requirements for the transportation of acrylonitrile are contained in the Hazardous Materials Transportation Act (PL 93-633), specifically, the Hazardous Materials Table (49 CFR 172.101). Acrylonitrile is classified as a flammable liquid. Requirements for the packaging of flammable liquids are contained in 49 CFR 173.119.

The outside packaging for acrylonitrile must contain these labels for flammable liquids and poisons:





Any motor vehicle, rail car, or freight container transporting acrylonitrile must display placards on the outside of the vehicle identifying the cargo as flammable. Labeling regulations are currently in force, but the placarding compliance date has been extended to July 1, 1978 (42 FR 58522).

The transport of acrylonitrile in a passenger-carrying aircraft, rail car or cargo vessel is prohibited. When shipped by cargo-only aircraft, a maximum of 1 quart of acrylonitrile may be contained in each package shipped. For cargo vessels, acrylonitrile may be stowed "on deck" or "under deck".

3. Environmental Protection Agency

a. Federal Insecticide, Fungicide, and Rodenticide Act

Under authority of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) (PL 94-140, PL 92-516) acrylonitrile (in a fumigant formulation with carbon tetrachloride) is classified for restricted use by the Environmental Protection Agency (Costle, 1978). The criteria influencing restriction were the hazard and accident history of both acrylonitrile and carbon tetrachloride. Procedures to be followed by registrants when using restricted use pesticides are set forth in the Federal Register of February

9, 1978 (43 FR 5782), about 5 months after proposed procedures were published (Sept. 1, 1977, 42 FR 44170; Costle, 1977).

There are 4 federally registered products containing acrylonitrile:

i) Stauffer Acritet 34-66-Fumigant

ii) ACRON 35

iii) SMCP Tetra-Fumigant

iv) B & G Fumi-ban

(Anon., 1978d). The manufacturers of these products have voluntarily cancelled these formulations according to the EPA Office of Special Pesticide Reviews. However, there are two manufacturers in Florida formulating an AN-CCl_4 fumigant.

b. Clean Air Act (PL 95-95)

As of January, 1978 acrylonitrile is not regulated under the Clean Air Act. A decision awaits information from EPA's Cancer Assessment Group and from Midwest Research Institute's Monitoring program (Anon., 1977n).

c. Federal Water Pollution Control Act

Acrylonitrile is one of 65 "Consent Decree" substances which are to be regulated under Section 307 of the Federal Water Pollution Control Act (PL 92-500). As a result of civil action, the EPA signed a consent agreement in June 1976 to establish effluent limitations for the discharge of these 65 substances. A water quality criteria is being drafted for acrylonitrile. This criterion is due to be published on June 20, 1978 and will provide for water to be of fishable and swimmable quality.

Effluent limitation guidelines for discharges associated with acrylic resin, acrylic fiber, and ABS and SAN manufacture (40 CFR 416) were suspended at 40 FR 21731.

d. Federal Water Pollution Control Act as Amended by the Clean Water Act of 1977 (P.L. 95-217)

Section 53. Under this section the EPA must establish effluent limitations for the 65 "Consent Decree" substances, which includes AN, no later than July, 1980. Other chemicals are also under consideration; EPA is working from a list of 129 "Priority Pollutants", which includes acrylonitrile.

Section 311. The EPA has designated 271 substances, including AN, as hazardous under Section 311 and subject to spill control effective June 12, 1978 (Costle, 1978b). Acrylonitrile (also 60 of the other substances) is considered "nonremoveable" from water after discharge. Also established was the "harmful quantity" for each substance, based primarily on LD_{50} values, when discharged into water; for AN, this was determined to be 100 pounds. In addition, civil penalties were established for discharge of each substance in "harmful quantities" or greater. For acrylonitrile the approximate rate of penalty is $8.80 per pound of spilled material. The penalty rate takes into account the "harmful quantity" as well as a physical/chemical/dispersal factor (whether the substance floats, sinks, mixes, precipitates or is miscible when discharged).

Section 504. Section 504 gives the Administrator of the E.P.A. emergency powers to take action in the event of a release of any pollutant into any media. The potential exists, therefore, for action in the event of a spill of acrylonitrile.

e. Solid Waste Act as Amended by the Resource Conservation and Recovery Act (Oct. 21, 1976)

Draft regulations of the amended Solid Waste Act call for the control of hazardous wastes. Criteria are being drawn up to regulate solid waste from specific industrial processes, with an effective date projected for mid-1979. In all likelihood, control of acrylonitrile will be affected under these process lists. Waste substances will be subject to toxicity and mutagenicity testing; control of acrylonitrile may also be affected as a result of this testing program.

4. Food and Drug Administration

The Food and Drug Administration regulates the use of acrylonitrile polymer and copolymer products when they are to be used in contact with food under 21 CFR 174-180.

The Food and Drug Administration amended food additive regulations (21 CFR 177.1020; 177.1030; 177.1040; 177.1050 and 177.1480) to eliminate the use of acrylonitrile copolymers to fabricate beverage containers (42 FR 48528-48544; Kennedy, 1977). The commissioner of Food and Drugs, Donald Kennedy, upheld an administrative law judge's decision that acrylonitrile copolymers used to fabricate beverage containers are food additives and have not been shown to be safe. The FDA ban on acrylonitrile went into effect on December 22, 1977. Monsanto has filed a petition for judicial review of FDA's decision (Anon., 1977o).

Acrylonitrile polymers and copolymers, which are considered indirect food additives, can be used in other non-beverage food contact uses including use in the following: adhesives; coatings; polyolefin films; paper and paperboard components (in contact with aqueous and fatty foods as a size promoter and retention aid; in contact with dry food); polymers and elastomers as components of single and repeated use food contact surfaces; and semi-rigid and rigid vinyl chloride plastics (21 CFR).

B. State Regulations

Agencies in 15 selected states (including those containing production and major end-use sites) were contacted about state-level regulations; responses appear in Table 53-56.

1. Workplace Standards

Of states responding to information requested on workplace exposure, all enforce the standards set by the Occupational Safety and Health Administration (Table 53).

2. Use as a Pesticide

States responding indicated acrylonitrile for fumigant use must be registered with the appropriate state office (e.g., in Ct., Pesticide Compliance Unit; in Missouri, Dept. of Agriculture; in Tenn., Division of Plant Industries). New Jersey, New York and Connecticut specifically indicated that acrylonitrile appears on state lists of restricted use pesticides (Table 54).

3. Water Quality

In most states, acrylonitrile is indirectly limited by general water quality standards (Table 55).

4. Air Emissions

Some states have established weight rate emission limitations (Table 55). For example, in Ohio, acrylonitrile is considered photochemically reactive, and as such, emissions are limited to 8 lbs./hour and 40 lbs./day per equipment, machine or article. However, if the source has a control device that is at least 85% efficient, the mass emission requirement is waived. In New York State, acrylonitrile is considered a toxic air contaminant when emissions exceed 1 lb./hour. In Texas, acrylonitrile is classified as a volatile carbon compound, with restrictions for volatile

Table 53

Regulations for Acrylonitrile Food Contact and Workplace Standards in Selected States; Asterisks(*) Indicate that Federal Standards are Followed, while Dashes Indicate no Response from State Agencies

	Food Contact	Workplace Standards
California	*	*
Connecticut	*	*
Delaware	*	*
Kentucky	-	-
Louisiana	-	-
Missouri	-	-
New Jersey	*	*
New York	*	-
Ohio	-	-
Pennsylvania	-	*
South Carolina	*	*
Tennessee	-	*
Texas	-	-

*federal standards followed; dashes indicate no response

Table 54

Pesticide Restrictions for Acrylonitrile in Selected States

State	Standard
California	no response
Connecticut	follows federal guidelines; AN is a restricted use pesticide in Conn.; user must be licensed by Pesticide Compliance Unit of Conn. Dept. Env. Prot.
Delaware	follows federal guidelines
Louisiana	no response
Missouri	requires registration with Missouri Dept. of Agriculture
New Jersey	AN is on N.J. Restricted Use list; user must have a N.J. Pesticide Applicator certification
New York	AN is a Restricted Pesticide under authority of N.Y. Environmental Conservation Law and Markets Law
Ohio	no response
Pennsylvania	registered under Pa. Pesticide Control Act
South Carolina	follows federal guidelines
Tennessee	all pesticides must be registered with the Division of Plant Industries
Texas	no response

Table 55

Water Standards for Acrylonitrile in Selected States

State	Standard
California	no response
Connecticut	no specific water quality standards or regulations; subject to case-by-case technical permit review by Water Compliance and Hazardous Substance Unit
Delaware	not specifically controlled
Kentucky	no response
Louisiana	case-by-case permit review
Missouri	no specific regulations
New Jersey	comply with Federal discharge requirements under FWPCA
New York	no water quality standards for AN
Ohio	general water quality standards apply; State Law: OAC-3745-1
Pennsylvania	general water quality standards apply
South Carolina	indirectly limited by general water quality criteria
Tennessee	general standards for toxic substances and organics apply
Texas	no response

Table 56

Air Standards for Acrylonitrile in Selected States

State	Standard
California	no response
Connecticut	emissions restricted to 8 lb/hr., 40 lbs/day for organic solvents; State Law: Section 19-508-20f(2)
Delaware	general air quality standards apply; State Law: Reg. 1-XXIII of Dept. Nat. Res. & Env. Control (for air pollution)
Kentucky	no response
Louisiana	no specific emission regulations
Missouri	no specific regulations
New Jersey	general restrictions for volatile organic substances apply and ambient air quality standards; State Law: NJEPA N.J. Adm. Code Title 7, Chp. 27
New York	AN considered at toxic air contaminant when emissions exceed 1 lb/hr.; State Law: Industrial Process Air Pollution Control Rule, part 212
Ohio	considered photochemically reactive (PR) by the Ohio Environmental Protection Agency. Emission requirements for PR materials is 8 lbs/hour and 40 lbs./day per equipment, machine or article. However, if the source has a control device (that is at least 85% efficient) the mass emission requirement is waived; State Law: OAC 3745-21-01(C)
Pennsylvania	no weight rate emission limitations for AN; standards for organic compounds apply for storage and loading; State Law: Pa. Air Pollution Control Act
South Carolina	no specific regulations
Tennessee	general process emission standards; State Law: 1200-3-7-.07
Texas	regulated as a volatile carbon compound; State Law: Reg. V

carbon storage, loading, and waste gas disposal listed in Regulation V of the Texas Air Control Board.

5. Food Contact

States responding indicated reliance on the regulations of the U.S.D.A. and F.D.A. (Table 52).

C. Foreign Countries

Agencies in several countries were contacted about acrylonitrile regulations. Their responses are summarized below (standards in U.S.S.R. and Bulgaria are from the literature).

1. United Kingdom

The workplace standards for acrylonitrile currently in force in the United Kingdom are:

TLV 20 ppm (45 mg/m^3) TLV = threshold limit value

STEL 30 ppm (68 mg/m^3) STEL = short-term exposure limit

The United Kingdom is currently re-evaluating acrylonitrile as a suspected carcinogen. In general, they follow closely the standards recommended by the American Conference of Governmental Industrial Hygienists (ACGIH). There are no water quality or air emission standards in the U.K. for acrylonitrile.

2. Canada

In Canada, occupational health falls under provincial, not federal, jurisdiction, so that in theory there could be 11 different standards. In general, provincial standards reflect ACGIH and/or OSHA recommendations.

There are no tolerance limits for acrylonitrile coming into contact with food, but Canadian studies are currently in progress to measure the extent of migration into food.

3. West Germany

In the Federal Republic of Germany, acrylonitrile is listed as a cancer-causing agent. No acceptable workplace standards can be set for such substances.

In waste gas, acrylonitrile cannot exceed 20 mg/m^3 (when flow rate is 0.1 kg/hr or more). There are no specific water quality standards for acrylonitrile.

4. Belgium

Acrylonitrile can be used as a fumigant only by persons who are licensed.

5. U.S.S.R. and Bulgaria

The mean acceptable concentration for acrylonitrile in the workplace is 0.5 mg/m^3 (1.1 ppm) in the U.S.S.R. and Bulgaria (Zotova, 1975; Spassovski, 1976).

D. Other Standards - Threshold Limit Value

The American Conference of Governmental Industrial Hygienists (ACGIH, 1971) recommended an 8 hour time weighted average of 20 ppm on the basis of animal exposure data and by analogy with the 10 ppm threshold limit value (TLV) for hydrogen cyanide. This had been the limit used by OSHA, until exposures were reduced to 2 ppm by the issuance of an Emergency Temporary Standard.

E. Current Handling Practices

1. Handling, Storage and Transport (American Cyanamid , 1974)

Because acrylonitrile presents health and fire hazards, caution must be exercised in its handling. Acrylonitrile drums should be stored on end no more than two high with the bungs up. To reduce the possibility of fire, acrylonitrile should be grounded electrically when being withdrawn from storage equipment. Top unloading is recommended for withdrawing acrylonitrile from tank cars or trucks.

Storage tanks are usually large enough to receive the entire contents of a tank car plus a working reserve (10 to 50%). American Cyanamid recommends that tanks be located above ground, resting on and anchored to concrete saddles surrounded by concrete or a padded earth dike. The dike should be large enough to contain the entire contents of the tank in case of tank failure. Insulation is not required (boiling pt. 77°C; freezing pt. -83°C).

Storage or handling containers should be thoroughly cleaned, as contaminated containers may initiate polymerization or decomposition. In particular, strong alkali or strong oxidizers (especially bromine) will initiate violent, exothermic polymerization.

Handling of acrylonitrile should be in a cool well-ventilated area, away from ignition sources.

Acrylonitrile is shipped by rail (40.4%), barge (1.7%) and truck (56.5%) (OHM-TADS, n.d.). Containers used for shipping have been described elsewhere in this report (II-C-4).

2. Personnel Exposure

American Cyanamid (1974) has suggested that the following protective equipment be available to workers: safety harness and life line, gas-tight safety goggles; industrial gas mask; neoprene or butyl rubber gloves, apron and boots; safety showers; fire extinguishers; and first-aid kit.

By authority of an Emergency Temporary Standard, OSHA requires that respiratory protection, protective clothing, and protective equipment (i.e., goggles) be available to employees (Bingham, 1978). Table 57 lists respiratory protection available for AN. OSHA also prescribed hygiene practices and medical surveillance necessary for compliance with the Emergency Temporary Standard. Workers exposed to AN must undergo a training and information program. Warning signs must be posted.

3. Accident Procedures

NIOSH suggested removing workroom spills by vacuum cleaning or by another method which does not increase the concentration of airborne acrylonitrile (NIOSH, 1977).

American Cyanamid (1974) suggests that small amounts of waste acrylonitrile resulting from leaks or spills can be removed to a remote location, poured onto dry sand or earth (preferably in a pit) then ignited. Such burning must comply with air pollution regulations.

The EPA Office of Hazardous Materials (OHM/TADS; n.d.) and the Coast Guard (DCT, 1974) suggested procedures to follow for larger spills. Fire and air authorities should be notified. The immediate area should be evacuated (EPA) or at least have restricted access (DOT). The Civil Defense should be warned of a potential explosion.

Carbon or peat may be used to adsorb acrylonitrile. Alkali solution will suppress HCN evolution and will help convert AN to the less toxic cyanate, but should be used with caution. EPA recommends leaving acrylonitrile in the nitrile form. Water containing less than 50 mg/l is subject to biological degradation.

The O and H Materials, Inc. (Finley, Ohio) drilled wells to pump acrylonitrile from contaminated groundwater to clean up a spill of 36,000 gallons in Gilford, Indiana (Manganaro, 1977, pers. comm.). This same

Table 57

Respiratory Protection for Acrylonitrile
(Bingham, 1978)

Concentration of AN or Condition of Use	Respirator Type
(a) Less than or equal to 20 ppm	(1) Any chemical cartridge respirator with organic vapor cartridge and half-mask; or (2) Any supplied air respirator with half-mask.
(b) Less than or equal to 100 ppm	(1) Any organic vapor gas mask; or (2) Any supplied air respirator with full facepiece; or (3) Any self-contained breathing apparatus with full facepiece.
(c) Less than or equal to 4,000 ppm	(1) Supplied air respirator in positive pressure mode with full facepiece, helmet, hood, or suit.
(d) Less than or equal to 20,000 ppm	(1) Supplied air respirator and auxiliary self-contained full facepiece in positive pressure mode; or (2) Open circuit self-contained breathing apparatus with full facepiece in positive pressure mode.
(e) Emergency entry into unknown concentrations or fire fighting.	(1) Any self-contained breathing apparatus with full facepiece in positive pressure mode.
(f) Escape	(1) Any organic vapor gas mask; or (2) Any self-contained breathing apparatus with full facepiece.

company adsorbed AN onto both peat moss and activated carbon to clean up a spill of 500-600 gallons in Benson, Kentucky (Patterson, 1977, pers. comm.).

Harsh (1978) described a method successfully used by the Ohio EPA to neutralize a spill of acrylonitrile. A tank car containing 133,300 pounds of acrylonitrile punctured and caught fire. The fire was put out and the next day most of the remaining acrylonitrile was pumped into a tank car and removed from the scene. However, samples of residual puddles near the spill site contained up to 7,231 mg/l AN. To prevent contamination of the groundwater the Ohio EPA began a neutralization process to act on the cyanide portion of the AN molecule. This process involved raising the pH of the AN contaminated area above 10 with lime, and then spraying chlorine over the area. Four days after the spill, lime (∿ 9600 pounds) was spread over the area using a bulldozer and shovels. That evening, 900 pounds of dry granular sodium hypochlorite were mixed with 1700 gallons of water and applied to the area. Samples taken after 2-4 days showed removal of 90 to 97+ percent of the acrylonitrile. Data for samples taken appear below:

Location	AN (mg/l) before treatment	AN (mg/l) after treatment	Removal (%)
Puddle north side of tracks	2,203	62.5	97+%
Puddle south side of tracks	7,231	13.1	99+%
Pool in woods	82-471	24	90-96%

VI. EXPOSURE AND EFFECTS POTENTIAL

Concern about the environmental exposure potential of acrylonitrile is warranted, especially in light of its potential carcinogenic effects. As discussed previously, environmental exposure can result during production, transport, end-use, and waste handling. For humans, the highest esposure potential is in the workplace; risks will be reduced substantially with compliance to the recently promulgated Emergency Temporary Standard.

Occupationally, up to 12,000 workers in the U. S. come into contact with acrylonitrile during the most dangerous phases of its use. However, considering all uses, about 125,000 workers are exposed (Anon, 1978c).

OSHA described several processes where employee contact to acrylonitrile would be most severe (Bingham, 1978). In the manufacture of acrylic fibers, exposure is greatest during wet-spinning when, after the fibers have coagulated, residual AN is driven off from the solvent.

Potential exposure to acrylonitrile occurs at several points during ABS resin manufacture, including: conveyance of AN from storage tanks; the blending, flocculation and drying areas; suspension and solution polymerization.

In nitrile rubber manufacture, risks occur especially when the polymerization product (with butadiene) is transferred to a tank where residual monomers are stripped. The resulting latex still contains high levels of unreacted monomer, thus exposure is also likely during the coagulation, washing and drying processes.

OSHA also assessed the risks to workers who produce products containing acrylonitrile. Handling of fibers is not a likely source of exposure. However, processing polymer latex is a potential source due to the high levels of unreacted monomer present.

In addition to occupational exposure, the possibility exists for general population exposure to acrylonitrile. However, no data are currently available to adequately assess this risk. On-going monitoring studies at producer and user facilities by the Midwest Research Institute will contribute information needed to perform a general population risk assessment (see section II-C). Based on limited monitoring data and estimates, losses of acrylonitrile to the atmosphere appear to be several times higher during polymerization operations (∿ 4100 tons AN emitted/yr) than monomer production (Mascone, 1978). During monomer production, small amounts of AN (0.00042-0.82 g AN/kg AN produced) have been identified from the absorber vent, incinerator stack, flare stack, product loading and storage facilities and from fugitive emissions (Table 15). Acrylonitrile is volatile and reactive so would not be expected to persist in the atmosphere; however, no studies were available on the atmospheric reactivity of AN.

Low level population exposure is possible from end-product use. OSHA indicates that there is no risk of residual acrylonitrile monomer migrating from finished acrylic or modacrylic fibers (Bingham, 1978). A. T. Kearney Inc. (1978) indicate little migration from finished consumer products. However, migration from SAN/ABS resins has been shown (summarized in Kennedy, 1977). The possibility exists for environmental contamination from resins of other finished products. The range of products made from acrylonitrile is large; the extent of acrylonitrile migration varies from product to product. Therefore, a general acceptable level of migration cannot be set

(Bingham, 1978). A possible source of aquatic contamination is from residual AN leaching from acrylamide used in water treatment and soil consolidation. However, no studies are available which assess this potential risk. Residual AN is about 1 ppm in polyacrylamide (Kearney, 1978) and 50-100 ppm in acrylamide monomer (Am. Cyanamid, 1977).

Transportation spills are another source of potential human contact with acrylonitrile. Human exposure at the scene of a spill would likely cause signs and symptoms known to occur in the workplace e.g., headache, mucous membrane irritation, vertigo, nausea, vomiting, and incoordination and dermatitis. Contamination of the drinking water might lead to central nervous system impairment, liver injury and hematological alterations.

Based on a study of A. D. Little (1974) and on actual reported spill incidents (Table 17) spills of acrylonitrile are most likely to occur along a rail route than by truck or barge transport. Monitoring data from actual spills are sparse. Acrylonitrile persisted for about a year or more in monitoring wells located near (within 100 feet) a tank car spill of 20,000 gallons of AN (Table 20). Initial levels of up to 35,000 mg AN/l were detected. No attempt at clean-up or containment was made until 108 days after the spill occurred; at that time 46-3520 mg AN/l were detected in monitoring wells. Levels decreased after some contaminated soil and groundwater was removed (Illinois EPA). In another spill (36,000 gallons onto farmland) the levels of AN in the groundwater increased for several months after each rainfall, indicating some short-term persistence. In a different spill, residual puddles initially contained up to 7,231 mg AN/l but a neutralization process reduced levels by 90% or more (Harsh, 1978).

The high levels of AN resulting from large spills are likely lethal to most microorganisms, severely hampering biodegradation and thus increasing persistence. Smaller levels (up to 50 mg AN/l), however, have been shown to be broken down biologically in laboratory tests. Unfortunately, no studies are available on the fate of AN under environmental conditions.

The potential for release of AN from deep wells, into which AN production wastewaters are injected, has not been assessed.

TECHNICAL SUMMARY

Acrylonitrile, CH_2CHCN, is a reactive, volatile chemical intermediate used mainly in the manufacture of fibers, resins, and synthetic rubber. A minor amount of AN is also used as a fumigant. More than 1.5 billion pounds of AN are produced annually, with a growth rate of 8-10% projected for the next few years (Anon, 1977b). Production occurs at six sites by four manufacturers (American Cyanamid Co.; E. I. DuPont de Nemours and Co., Inc.; Monsanto Co.; Vistron Corporation). All produce acrylonitrile by the catalytic vapor phase oxidation of propylene and ammonia (ammoxidation of propylene); by-products include acetonitrile and hydrogen cyanide.

Small amounts of acrylonitrile enter the environment during several phases of its production. Other sources of potential environmental contamination include transportation losses, end-product manufacture and end-product use.

Limited data on environmental exposure indicate that up to 50 mg AN/1 (highest level tested) in aqueous systems are subject to biological degradation, particularly if the microorganisms are acclimated. Due to its chemical reactivity and biodegradability, acrylonitrile is expected to have a short residence time in the environment (Nat'l. Acad. Sci., 1975).

Recent evidence indicates that acrylonitrile exposure may present increased carcinogenic, teratogenic, and mutagenic risks. A preliminary study by DuPont revealed excess cancer incidence and cancer mortality among workers exposed to acrylonitrile at a fiber plant in Camden, S. C. (O'Berg, 1977). In rats, preliminary data from two studies sponsored by the Manufacturing Chemists Association, show that prolonged exposure to acrylonitrile results in higher tumor incidence (including carcinomas) (Norris, 1977; Clark, 1977 and 1978). In one study rats were exposed to vapor levels of 20 or 80 ppm AN 6 hours/day for 5 days/week; in another study rats consumed 35, 100 or 300 mg/l (ppm) AN in the drinking water. Interim sacrifices after one year revealed tumors of the stomach, central nervous system and Zymbal gland of the ear canal in rats receiving AN in the drinking water at 100 or 300 mg/l. Rats exposed to 80 ppm AN vapor for 2 years developed tumors of both the central nervous system and ear canal and mammary region masses; at 20 ppm, there was an increase in subcutaneous masses of the mammary region. Maltoni et al. (1977) found AN to have a "borderline oncogenic effect" in rats ingesting (5 mg/kg, 3x/wk) or inhaling (87, 43, 22, or 11 mg/m^3, 4 hr/day, 5-days/wk) the compound for 52 weeks.

In another study, maternal and fetal toxicity occurred in gravid rats receiving 25 or 65 mg AN/kg orally during gestation (Murray et al., 1976). Embryotoxic effects have been shown for mice (Scheufler, 1976). Acrylonitrile was positively mutagenic in some bacterial assays, but not others (e.g., SRI, 1976; Litton Bionetics, 1975; Milvy and Wolff, 1977; Venitt et al., 1977).

Acrylonitrile is toxic in humans by inhalation, ingestion, and skin contact. Several cases of acrylonitrile intoxication have been reported for industrial exposure in synthetic rubber manufacture and polymerization (Wilson, 1944; Wilson et al., 1948), and for accidental exposure (Dudley and Neal, 1942; Sartorelli, 1966), including fumigant use (Grunske, 1949; Radimer et al., 1974). Acute vapor exposure can cause headache, mucous membrane irritation, vertigo, vomiting and incoordination. A few cases of anemia and jaundice have been attributed to acrylonitrile (Wilson, 1944). Fumigant exposure has resulted in toxic epidermal necrolysis and, in a few cases, death. Direct skin contact results in irritation and diffuse erythema. Russian and Japanese epidemiological studies indicate that long-term exposure may result in hematological alterations, mild liver injury, and central nervous system impairment (Sakurai and Kusumoto, 1972; Zotova, 1975; Shustov, 1968).

In mammals, lethal doses of acrylonitrile generally result in altered breathing, incoordination, weakness, convulsions, and coma, followed by death. There has been some disagreement about whether breathing is initially stimulated before becoming shallow (as occurs in cyanide poisoning) (c.f. Dudley and Neal, 1942; Paulet et al., 1966). Depending on the dose and route, death usually occurs within 24 hours. At low doses, recovery is usually complete, without apparent after effects. Signs vary less be-between routes of administration than between dose and species. In laboratory mammals, acute oral LD_{50} values range from 25 to 128 mg AN/kg while acute parenteral values range from 15 to 130 mg AN/kg. By both route, mice are most sensitive; guinea pigs, and rats are generally least sensitive. Inhalation studies show dogs to be most sensitive to acrylonitrile (Dudley and Neal, 1942). Direct skin contact results in erythema. Dermal LD_{50} values range from 25 to 128 ml AN/kg for guinea pigs and rabbits.

Predominant effects of acute doses of acrylonitrile to laboratory animals include: central and peripheral nervous system damage (Hashimoto and Kanai, 1965; Paulet et al., 1966); bilateral adrenal apoplexy and necrosis (Szabo and Selye, 1971; Szabo et al., 1976); lowered levels of nonprotein sulfhydryl content of the kidney (Wisniewska-Knypl et al., 1970; Szabo et al., 1977), liver (Dinu and Klein, 1976; Vainio and Mäkinen, 1977), lung (Szabo et al., 1977) and brain (Hashimoto and Kanai, 1972); and hemorrhagic areas of the lungs and liver (e.g., Dudley and Neal, 1942; Jedlicka et al., 1958).

Long-term effects of acrylonitrile have been described for rats and dogs. Rats ingesting acrylonitrile in the drinking water (35, 85, 210, or 500 mg/l AN) for 90 days showed no treatment-related pathologic alterations; decreased body weight gain and increased liver to body weight ratios occurred among rats receiving the two higher doses (Humiston et al., 1975). Incorporation of 0.05 or 0.2% AN in the drinking water of rats for 21 to 60 days affected mineralcorticoid and glucocorticoid producing cells of the adrenal cortex (Szabo et al., 1976). Subacute ingestion of low levels of acrylonitrile in rats caused dose dependent increases in liver glutathione levels (Szabo et al., 1976). Subacute injection and inhalation may adversely affect the nervous system, liver, and kidneys and retard growth, depending on the dose.

Rats ingesting acrylonitrile for 13 months (35-300 mg/l AN in the drinking water) showed decreased water consumption, but normal blood chemistry and cell levels. At the higher doses, food consumption and body weight gain were reduced. Dogs also showed reduced food and water consumption when given acrylonitrile in the drinking water (200 or 300 mg/l for up to 6 mo.). Most dogs at these levels either died spontaneously or were euthanized, showing terminal depression, lethargy, weakness, emaciation and pneumonia.

In laboratory organisms, acrylonitrile is broken down to cyanide (which is oxidized to thiocyanate) and reacts with sulfhydryl groups by cyanoethylation. Minor pathways are either unconfirmed or not positively identified. The metabolism of acrylonitrile appears to be species, route and dose dependent (Gut et al., 1975; Young et al., 1977). The toxic action of acrylonitrile may be due partly to cyanide formation but is also probably due to the direct action of acrylonitrile. However, there may be substantial species differences (i.e., cyanide-mediated toxicity is likely in mice but doubtful in rats). There has been considerable disagreement about the mechanism of action.

Acrylonitrile is toxic to fish and other aquatic species. The 24-hour median tolerance limit values for several species of freshwater fish ranges from 25-45 mg AN/l (ppm). Concentrations lethal to shrimp, aquatic insect larvae and insects are known (~ 1-50 mg/l).

The current workplace exposure is limited by the Occupational Safety and Health Administration to 2 ppm (a time-weighted average over 8 hours). Acrylonitrile is classified as a restricted use pesticide.

BIBLIOGRAPHY

Ageyeva, T. S., (1970) ["The Condition of the Metabolism of Mediating Substances in Workers Producing Acrylonitrile,"] Tr. Sarat Med. Inst. 71-88:10-13. (Russian).

AIHA, (1970) "Acrylonitrile," Am. Ind. Hyg. Assoc. J., July-August, 1970:529-531.

American Conference of Governmental Industrial Hygienists, (1971) Documentation of the Threshold Limit Values for Substances in Workroom Air, 3rd Edit., Cincinnati, Ohio, p. 6.

American Cyanamid Co., (1959) The Chemistry of Acrylonitrile, Second Edit., Am. Cyanamid Co., Petrochem. Dep., New York, 272 pp.

American Cyanamid Co., (1974) "Handling Storage - Analyses of Acrylonitrile," Am. Cyanamid Co., Process Chem. Dep., Wayne, New Jersey, 42 pp.

American Cyanamid Co., (1976) "Material Safety Data Sheet: Acrylonitrile," Wayne, N. J.

American Cyanamid, (1977) In Response to OSHA's Request for Information on Acrylonitrile [42FR:33043]. Letter to U.S. Dept. of Labor-OSHA, Docket Officer.

Anon., (1973) "New Catalytic Route to Acrylamide," Chem. Eng., 80(27): 68-69.

Anon., (1974) "Chemical Profile: Acrylonitrile," Chem. Mark. Rep., 205(12):9.

Anon., (1975) "Acrylonitrile (Sohio Process)," Hydroc. Proc., Nov. 1975:108.

Anon., (1976) "Technological Export of AN Catalyst," Chem. Econ. Eng. Rev., 8(9):59.

Anon., (1976) "Propylene Supply Tightens, Prices Rise," Chem. and Eng. News, Sept. 13, 1976:10.

Anon., (1977a) "Nitto Chem. and Sohio Reach Catalyst Tie-Up," Jpn. Econ. J., 15:8.

Anon., (1977b) "Chemical Profile: Acrylonitrile," Chem. Mark. Rep., 211(2):9.

Anon., (1977c) "Acrylo Growth Won't be Bottled Up," Chem. Week, March 9, 1977:30-31.

Anon., (1977d) "Acrylonitrile Pricing U.S.," Chem. Mark. Rep., 6(24):20.

Anon., (1977e) "Propylene Demand," Chem. Eng., June 6, 1977:137-138.

Anon., (1977f) "Chemical Profile: ABS Resins," Chem. Mark. Rep., 211(13):9.

Anon., (1977g) "ABS Project Scheduled," Chem. Mark. Rep. 211(22):3.

Anon., (1977h) "Plastics Corner," J. Commer., March 3, 1977:5.

Anon., (1977i) "SAN Producers Ranks Decline," J. Commer., May 16, 1977:5.

Anon., (1977j) "ABS '77: New Supplier, New Grade, 100,000-Plus Tons of New Capacity," Mod. Plast., 54(2):16.

Anon., (1977k) "Acrylonitrile Use Growing in Non-Beverage Applications," Mod. Packag., July, 1977:5-7.

Anon., (1977 l) "FDA Bans AN Bottles," Chem. Wk., Sept. 28, 1977:22.

Anon., (1977m) "OAOPS Asks CAG to Do Risk Assessments on Acrylonitrile, Perchloroethylene," Pestic. Toxic Chem. News, Dec. 7, 1977:24.

Anon., (1977n) "Some Additional Chemicals Slated for Pre-RPAR Reviews," Pest. Toxic Chem. News, Dec. 7, 1977:12-13.

Anon., (1977o) "Government Concentrates: Monsanto Challenges FDA on Acrylonitrile," Chem. and Eng. News, Nov. 28, 1977:11.

Anon., (1977p) "Monsanto Launches its own Acrylonitrile Rat Feeding Studies," Chem. Wk., August 3, 1977:31-32.

Anon., (1978a) "U. S. Plastics Sales Data; 1977 vs. 1976," Mod. Plast., Jan., 1978:49-53.

Anon., (1978b) "Resin Supply and Price Status," Mod. Plast., Jan., 1978:54-55.

Anon., (1978c) "OSHA Orders Emergency Rule for Acrylonitrile," Wall St. Jour., Jan. 17., 1978:6.

Anon., (1978d) "EPA Restricted Use Pesticide Product Listing," Chem. Reg. Rep., 1(48):1677.

Anon., (1978e) "Emergency Standard Stayed by Sixth Circuit Appeals Court," Chem. Reg. Rep., 1(50):1836.

Anton'ev, A. A. and Rogailin, V. I., (1970) ["Professional Dermatoses Caused by Acrylonitrile and Their Prophylaxis"] Tr. Permsk. Gos. Med. Inst., 99:103-106. (Russian).

Baker, R. A., (1963) "Threshold Odors of Organic Chemicals" J. Am. Water Works Assoc., 55(7):913-916.

Balda, B. R., (1975) ["Acrylonitrile as a Contact Allergen"] Hautarzt., 26:599-601. (German).

Bamford, C. H. and Eastmond, G. C., (1964) "Acrylonitrile Polymers," Encycl. Polym. Sci. and Technol., 1:374-425.

Bandt, H.-J., (1953) ["Acrylonitrile as an Effluent,"] Z. Fisch. 2:457-461. (German).

Barnes, J. M., (1970) "Effects on Rats of Compounds Related to Acrylamide," Brit. J. Ind. Med., 27(2):147-149.

Barnhart, T., (1968) "Rubber Compounding," Kirk-Othmer Encyl. Chem. Technol. 2nd edit., 17:543-545.

Benes, V. and Cerná, V., (1959) ["Acrylonitrile: Acute Toxicity and Mechanism of Action,"] J. Hyg. Epidemiol. Microbiol. Immunol., 3:106-116. (German).

Benes, V. and Sram, R., (1969) "Mutagenic Activity of Some Pesticides in *Drosophila melanogaster*," Ind. Med. Surg., 38(12):442-444.

Berck, B., (1960) "Fumigant Residues: Retention of Acrylonitrile and Carbon Tetrachloride by Shelled Walnuts Fumigated with Acrylon," J. Agric. and Food Chem., 8(2):128-131.

Berck, B., (1975) "Analysis of Fumigants and Fumigant Residues," J. Chromatogr. Sci., 13(6):256-267.

Bikales, N. M., (1973) "Preparation of Acrylamide Polymers," Polymer Science and Technology, vol. 2:213-225.

Bikales, N. M. and Kolodny, E. R., (1963) "Acrylamide," Kirk-Othmer Encycl. of Chem. Technol., 2nd Edit., 1:274-284.

Bingham, E., (1978) "Emergency Temporary Standard for Occupational Exposure to Acrylonitrile (Vinyl Cyanide); Notice of Hearing," Fed. Regist., 43(11):2586-2607.

Bond, E. J. and Buckland, C. T., (1976) "Control of Insects with Fumigants at Low Temperatures: Toxicity of Mixtures of Methyl Bromide and Acrylonitrile to Three Species of Insects," J. Econ. Entomol., 69:725-727.

Borchardt, von K., Franzen, E. and Hartmann, B., (1970) ["Acute Oral Intoxication with Acrylonitrile in Animals,"] Z. Fuer Die Gesamte Hyg. Ihre Grenzgeb., 16:316-319. (German).

Borg Warner Chemicals, (1977) In Response to OSHA's Request for Information on Acrylonitrile [42FR:33043]. Letter to U. S. Dep. of Labor - OSHA, Docket Officer.

Bott, B., Firth, J. C. and Jones, T. A., (1969) "Evolution of Toxic Gases from Heated Plastics," Br. Polym. J., 1:203-204.

Brewer, W. E., (1976) "90-day Subacute Vapor Inhalation Toxicity Study with Acrylonitrile in Beagle Dogs, Albino Rats and Albino Mice," Industrial Bio-Test No. 74-42, prepared for the Monsanto Co.

Brieger, H., Rieders, F. and Hodes, W. A., (1952) "Acrylonitrile: Spectrophotometric Determination, Acute Toxicity, and Mechanism of Action," Indus. Hyg. and Occup. Med., 6:128-140.

Burg, S. P. and Burg, E. A., (1967) "Molecular Requirements for the Biological Activity of Ethylene," Plant Physiol., 42:144-152.

Carpenter, C. P., Smyth, H. F. and Pozzani, V. C., (1949) "The Assay of Acute Vapor Toxicity, and the Grading and Interpretation of Results on 96 Chemical Compounds," J. Industr. Hyg. Toxicol., 31(6): 343-346.

Chaigneau, M. and LeMoan, G., (1974) ["Study of the Pyrolysis of Plastic Materials. 8 Polyacrylonitrile and Copolymers,"] Ann. Pharm. Fr., 32:484-490. (French).

Cherry, A. B., Gabaccia, A. J. and Senn, H. W., (1956) "The Assimilation Behavior of Certain Toxic Organic Compounds in Natural Water," Sewage Ind. Waste, 28(9):1137-1146.

Clark, A. C., (1977) unpublished letter to D. Costle, Administrator EPA, 4/11/77 concerning MCA-sponsored studies.

Clark, A. C., (1978) unpublished letter to D. Costle, Administrator EPA, 2/22/78 concerning MCA-sponsored studies.

Clean Air Act Amendments of 1977, PL 95-95, Approved August 7, 1977.

Clean Water Act of 1977, PL 95-217, Approved December 27, 1977.

Clive, D. and Spector, F. S., (1975) "Laboratory Procedure for Assessing Specific Locus Mutagens at the TK Locus in Cultured L_{5178}Y Mouse Lymphoma Cells," Mut. Res., 31:17-29.

Collins, T. F. V., (1977) Written Testimony in the Matter of Acrylonitrile Copolymers used to Fabricate Beverage Containers, Docket No. 76N-0070, Exhibit G-82.

Cornish, H. H., Kolman, J. H. and Barth, M. L., (1975) "Experimental Toxicology of Pyrolysis and Combustion Hazards," Environ. Health Perspect., 11:191-196.

Costle, D. M., (1977) "Classification by Regulation of Uses of Pesticide Products for Restricted Use. Optional Procedures and Lists of Certain Pesticide Products," Fed. Regist., 42(170):44170-44189.

Costle, D. M., (1978a) "Optional Procedures for Classification of Pesticide Uses by Regulation; Pesticide Use Restrictions," Fed. Regist., 43(28):5782-5791.

Costle, D. M., (1978b) "Water Programs: Hazardous Substances," Fed. Regist., 43(40):10474-10508.

Cueto, C., (1978) Prepared Statement for OSHA Public Hearing on Proposed Standard for Occupational Exposure to AN, March 21, 1978; exhibit no. 21.

Czajkowska, T., (1971) ["Excretion of Certain Metabolites Upon Single Administration of Acrylonitrile,"] Med. Pr., 22(4):381-385. (Polish).

Dahm, D. J., (1977) "Identification of Metabolites of Acrylonitrile," Testimony Before FDA *in* Monsanto Co. (1977b) *op. cit.*, Appendix 4:A-1 to A-19.

Daugherty, F. M. and Garrett, J. T., (1951) "Toxicity Levels of Hydrocyanic Acid and Some Industrial By-Products," Texas J. Sci., 1951(3):391-396.

Davis, J. H., Davies, J. E., Americo Raffonelli, R. S. and Reich, G., (1973) "The Investigation of Fatal Acrylonitrile Intoxications," Pesticides and the Environment: A Continuing Controversy, Intercontinental Med. Book Corp. 2:547-556.

Department of Transportation, (1974) "Acrylonitrile," CHRIS Hazardous Chemical Data, Dep. of Transp. Coast Guard, C-G-446-2.

DiGeronimo, M. J. and Antoine, A. D., (1976) "Metabolism of Acetonitrile and Propionitrile by Nocardia," Appl. Environ. Microbiol. 31(6):900-906.

Dinu, V. and Klein, R., (1976) ["Catalase Activity, Glutathione and Lactic Acid Levels in Rats Acutely Intoxicated by Acrylonitrile,"] J. Pharmacol., 7(2):223-226. (French).

Dorigan, J., Fuller, B. and Duffy, R., (1976) "Scoring of Organic Air Pollutants Chemistry, Production and Toxicity of Selected Synthetic Organic Chemicals (Chemicals A-C)," MITRE Tech. Rep. MTR-7248.

Dow Badische Co., (1977) In Response to OSHA's Request for Information on Acrylonitrile, [42FR:33043] Letter to U. S. Dept. of Labor - OSHA, Docket Officer.

Dow Chemical Co., (1977) In Response to OSHA's Request for Information on Acrylonitrile [42FR:33043] Letter to U. S. Dep. of Labor - OSHA, Docket Officer.

Dudley, H. C. and Neal, P. A., (1942) "Toxicology of Acrylonitrile (Vinyl Cyanide) I. A. Study of the Acute Toxicity," J. Industr. Hyg. Toxicol., 24:27-36.

Dudley, H. C., Sweeney, T. R. and Miller, J. W., (1942) "Toxicology of Acrylonitrile (Vinyl Cyanide) II. Studies of Effects of Daily Inhalation," J. Industr. Hyg. Toxicol., 24:255-258.

DuPont Co., (1977b) In Response to OSHA's Request for Information on Acrylonitrile [42FR:33043] Letter to U. S. Dep. of Labor - OSHA, Docket Officer.

DuPont Co., (1977b) In Response to OSHA's Request for Information on Acrylonitrile [42FR:33043] Unpubl. Letter to U. S. Dep. of Labor - OSHA, Docket Officer.

Efremov, A. M., (1976) ["Study of the Biotransformation of Acrylonitriles in Animals,"] Zdravookhr. Beloruss. (7):85-86. (Russian).

Environmental Protection Agency, (1977) "Status Assessment of Toxic Chemicals. 1. Acrylonitrile," 1-33.

FDA, (1977) "Determination of Acrylonitrile in Food Simulating Solvents" Food and Drug Adm. Bur. of Foods, 4 pp.

Federal Insecticide, Fungicide and Rodenticide Act, PL 94-140, Approved Nobember 28, 1975; PL 92-516, Approved October 21, 1972.

Federal Water Pollution Control Act Amendments of 1972, PL 92-500, Approved October 18, 1972.

Ferin, J., Urbankovc, G and Vlekcva, A., (1961) ["Hygienic and Toxicological Problems of Acrylonitrile and Dimethylformamide,"] Prac. Lek., 8-9(13):466-468. (Polish).

Finklea, J. F., (1977) "Current Intelligence Bulletin: Acrylonitrile," Dep. of Health, Educ. and Welfare, Nat'l. Inst. for Occup. Saf. and Health.

Finney, D. J., (1952) Probit. Analysis. Cambridge Univ. Press, N. Y., pp. 123-159.

Fitzgibbons, W. O., Schwerko, E. M. and Brainard, A. H., (1973) "Deep Well Disposal of Acrylonitrile-Process Waste Water," U. S. Pat. 3,734,943:3 pp.

Fugate, W. O., (1963) "Acrylonitrile" Kirk-Othmer Encycl. Chem. Technol. 2nd Edit., 1:338-351.

Ghiringhelli, L., (1954) ["Acrylonitrile: Toxicity and Action,"] Med. Del Lav. 45(5):305-312. (Italian).

Giacin, K., Gilbert, S. and Antoine, A. D., (1973) "Utilization of Acrylonitrile-based Polymers and Related Monomers by Soil Fungi," Am. Soc. for Microbiol. Abstr. of the Annu. Meet., 170.

Gisclard, J. B., Robinson, D. B. and Kuczo, P. J., Jr., (1958) "A Rapid Empirical Procedure for the Determination of Acrylonitrile and Acrylic Esters in the Atmosphere," Am. Ind. Hyg. Assoc. J., 19: 43-45.

Glass, E. H. and Crosier, W. F., (1949) "The Viability of Seeds Fumigated with an Acrylonitrile-Carbon Tetrachloride Mixture," J. Econ. Ent., 42 (4):646-649.

Goodrich Co., B. F., (1977) In Response to OSHA's Request for Information on Acrylonitrile, [42FR:33043] Letter to U.S. Dep. of Labor - OSHA, Docket Officer.

Graczyk, J., (1973) ["Effects of Adrenaline, Noradrenaline and Acetylcholine on Blood Pressure in Acute Experimental Acrylonitrile Poisoning,"] Med. Pr., 24(2):151-158. (Polish).

Graham, J. D. P., (1965) "Hydroxycobalamin as an Antidote to Acrylonitrile," Toxicol. Appl. Pharm., 7:367-372.

Green, M. L. H., Muriel, W. J. and Bridges, B. A., (1976) "Use of Simplified Fluctuation Test to Detect Low Levels of Mutagens," Mut. Res., 38:33-42.

Grunske, F., (1949) ["Ventox and Ventox - Poisoning,"] Dtsch. Med. Wschr. 74:1081-1083. (German).

Gut, I., Nerudova, J., Kopecky, J. and Holecek, K., (1975) "Acrylonitrile Biotransformation in Rats, Mice, and Chinese Hamsters as Influenced by the Route of Administration and by Phenobarbital, SKF 525-A, Cysteine, Dimercaprol, or Thiosulfate," Arch. Toxicol., 33:151-161.

Hall, M. E. and Stevens, J. W., Jr., (1977) "Spectrophotometric Determination of Acrylonitrile," Anal. Chem., 49(14):2277-2280

Handin, R. I. and Szabo, S., (1977) "Blood Coagulation Changes and Vascular Damage in the Etiology of Acrylonitrile Induced Adrenal Apoplexy," Fed. Proc., 36(3):397.

Harsh, K. M., 1978 "*In situ* Neutralization of an Incident Involving an Acrylonitrile Tank Car," Proc. of the 1978 National Conference of the Control of Hazardous Material Spills, Miami Beach, April 1978.

Hashimoto, K. and Kanai, R., (1965) "Studies on the Toxicology of Acrylonitrile Metabolism, Mode of Action and Therapy," Ind. Health, 3(1-2):30-45.

Hashimoto, K. and Kanai, R., (1972) "Effect of Acrylonitrile on Sulphydryls and Pyruvate Metabolism in Tissues," Biochem. Pharmacol., 21(5):635-640.

Haskell Laboratory, (1975) "*In Vitro* Microbial Mutagenicity Studies of Acrylonitrile" Report No. 351-75, E. I. DuPont de Nemours and Co. Haskell Lab. for Toxicology and Industrial Medicine.

Haslam, J. and Newlands, G., (1955) "Determination of Acrylonitrile in Air," Analyst, 180:50-53.

Hazardous Materials Transportation Act, PL 93-633, Approved January 3, 1975.

Henderson, C., Pickering, G. H. and Lemke, A. E., (1961) "The Effect of Some Organic Cyanides (Nitriles) on Fish," Proc. 15th Ind. Waste Conf., En. Bull. 45(2):120-130.

Heuser, S. G. and Scudmore, K. A., (1968) "Methods, Apparatus: New Product Research, Process Development and Design," Chem. and Ind. (London), 34:1154-1157.

Hilado, C. J., Slattengren, C. L., Furst, A., Kourtides, D. A. and Parker, J. A., (1976) "Relative Toxicity of Pyrolysis Products of Some Synthetic Polymers," J. Combust. Toxicol., 3(3):270-283.

Hoffman, P., Kleine, D. and Franzen, E., (1976) ["On the Proof of Acrylonitrile Exposure: Detoxification of Acrylonitrile by Coupling with D-Glucuronic Acid,"] Z. Gesampte Hyg. Ihre Grenzgeb., 22(5): 310-312. (German).

Holker, J. R., (1975) "Chapter 9, Fibers *in* Tedder, J. M., Nechvatal, A. and Jubb, A. H. (eds.) Basic Organic Chemistry Part 5: Industrial Products. John Wiley and Sons, New York, pp. 289-291.

Hovious, J. C., Waggy, G. T. and Conway, R. A., (1973) "Identification and Control of Petrochemical Pollutants Inhibitory to Anaerobic Processes," NTIS Rep. Number-PB-222 287.

Hughes, L. N. (1974) Unpub. letter to A. W. Polich concerning the Greater Peoria Sanitary District (Ill.) tests on AN. *in* Ill. Environmental Protection Agency *op. cit.*

Hughes, T. W. and Horn, D. A., (1977) "Source Assessment: Acrylonitrile Manufacture (Air Emissions)" NTIS Rep. Number-PB-271 969.

Humiston, C. G., Frauson, L. O., Quast, J. F. and Norris, J. M., (1975) "A 90-day Oral Toxicity Study Incorporating Acrylonitrile in the Drinking Water of Rats," Toxicology Research Laboratory, Dow Chemical U.S.A., Midland, Mich., prepared for the Manufacturing Chemists Association.

Idol, J. D., Jr., (1974) "Acrylonitrile Polymers in Prospect and Retrospect," Applied Polymer Symposium 25: Acrylonitrile in Macromolecules, John Wiley and Sons, Inc., 1-18.

Illinois Environmental Protection Agency, file on Acrylonitrile Spill of 12/23/74 near Mapleton, Ill.

Jackson, S. and Brown, V., (1970) "Effect of Toxic Wastes on Treatment Processes and Water Courses," Wat. Poll. Control, 69:292-303.

Jacobs, H. W. and Syrjala, R. J., "The Use of Infrared Analyzers for Monitoring Acrylonitrile," Am. Ind. Hyg. Assoc. J., in Press Feb., 1978.

Jaeger, R. J., Conolly, R. B. and Murphy, S. D., (1974) "Toxicity and Biochemical Changes in Rats after Inhalation Exposure to 1,1-Dichloroethylene, Bromobenzene, Styrene, Acrylonitrile or 2-Chlorobutadiene," Toxicol. Appl. Pharmacol., 29(1):81.

Jedlicka, V., Pasek, A. and Gola, J., (1958) "Pesticides in Foods. III. Acrylonitrile as a Food Insecticide," J. Hyg. Epidemiol. Micro. Immun., 1:116-125.

Johnston, R. V., Schwetz, B. A., Middleton, J. J., Humiston, C. G. and Lisowe, R. W. (n.d.) "Cytogenetic Effects of Acrylonitrile (AN) on Rat Bone Marrow Cells," Toxicology Research Laboratories, Midland, Mich., 5 pp.

Kanai, R. and Hashimoto, K., (1965) "Determination of Acrylonitrile, Cyanide and Thiocyanate in Biological Materials," Ind. Health, 3:47.

Kato, A. and Yamamura, K., (1976) "Treating Waste Water Containing Nitriles and Cyanides," U.S. Pat., 3,940,332.

A. T. Kearney, Inc., (1978) "Assessment of Acrylonitrile Contained in Consumer Products: Draft Final Report," U.S. Consumer Product Safety Commission, Task No. 1014k.

Kennedy, D., (1977) "Indirect Additives: Polymers. Acrylonitrile Copolymers Used to Fabricate Beverage Containers," Final Decision," Fed. Regist., 42(185):48528-48544.

Kihlman, B. A., (1961) "Cytological Effects of Phenylnitrosamines I. The Production of Structural Chromosome Changes in the Presence of Light and Acridine Orange," Radiat. Bot., 1:35-42.

Knobloch, K., Szendzikowski, S. and Czajkowska, T., (1972) ["Chronic Toxicity of Acrylonitrile,"] Med. Pr., 23(3):243-257. (Polish).

Knobloch, K., Szendzikowski, S., Czajkowska, T. and Krysiak, B., (1971) ["Experimental Studies upon Acute and Subacute Toxicity of Acrylonitrile,"] Med. Pr., 22(3):257-269. (Polish).

Krysiak, B. and Knobloch, K., (1971) ["The Effect of Acrylonitrile Upon the Central Nervous System,"] Med. Pr., 22(6):601-610. (Polish).

Lank, J. C., Jr., (1969) "Effect of Acrylonitrile on Anaerobic Digestion of Domestic Sludge," Master's Thesis-Univ. of Idaho Graduate School, March 1970:76 pp.

Lawton, A. H., Sweeney, T. R. and Dudley, H. C., (1943) "Toxicology of Acrylonitrile (Vinyl Cyanide): III. Determination of Thiocyanates in Blood and Urine," J. Industr. Hyg. Toxicol., 25:13-19.

Lindgren, D. L., Vincent, L. E. and Krohne, H. E., (1954) "Relative Effectiveness of Ten Fumigants to Adults of Eight Species of Stored-product Insects," J. Econ. Ent., 47(5):923-926.

A. D. Little, Inc., (1974) "A Modal Economic and Safety Analysis of the Transportation of Hazardous Substances in Bulk," Final Rep. NTIS Rep. COM-74-11271, 264 pp.

Litton Bionetics, Inc., (1975) "Mutagenic Evaluation of Compounds MCA 730," LBI Project #2547, prepared for the Manufacturing Chemists Association.

Litton Bionetics, Inc., (1976) "Mutagenicity Evaluation of MCA 730-Final Report," LBI Project No. 2548, prepared for the Manufacturing Chemists Association.

Livingston, R., (1977) memo to T. Brown 2/18/77 (Exhibit #M-76). FDA Hearing in the Matter of AN Copolymers used to Fabricate Beverage Containers, Docket No. 76N-0070.

Lorz, H., (1950) ["On Percutaneous Poisoning with Acrylonitrile (Ventox),"] Dtsch. Med. Wschr., 75:1087-1088. (German).

Loveless, A., (1951) "Qualitative Aspects of the Chemistry and Biology of Radiomimetic (mutagenic) Substances," Nature (London), 167:338-342.

Loveless, L. E., Spoerl, E. and Weisman, T. H., (1954) "A Survey of Effects of Chemicals on Division and Growth of Yeast," J. Bacteriol., 68:637-644.

Lowenbach, W., Schlesinger, S. and King, J., (1978) "Toxic Pollutant Identification: Acrylonitrile Manufacture," EPA-IMPQE series 02178-03, 160 pp.

Ludzack, F. J., Schaffer, R. B. and Bloomhuff, R. N., (1959) "Experimental Treatment of Organic Cyanides by Conventional Sewage Treatment Processes," Proc. 14th Ind. Waste Conf., Purdue Univ., 547-565.

Ludzack, F. J., Schaffer, R. B., Bloomhuff, R. N. and Ettinger, M. B., (1958) "Biochemical Oxidation of Some Commercially Important Organic Cyanides. I: River Water Oxidations," Proc. 13th Ind. Waste Conf., 297-312.

Madorsky, S. L., (1964) "VIII. Acrylonitrile Polymers; 1. Polyacrylonitrile," Thermal Degradation of Organic Polymers, Interscience Publ., 195-202.

Madson, F., (1978). Written testimony (Exhibit 18) Vistron Corp. et al. V OSHA et al., Docket No. 78-3026 dated 2/22/78.

Magos, L., (1962) "A Study of Acrylonitrile Poisoning in Relation to Methaemoglobin-CN Complex Formation," Brit. J. Industr. Med., 19: 283-286.

Mallette, F. S., (1943) "Industrial Hygiene in Synthetic Rubber Manufacture," Indus. Med., 12:495-499.

Maltoni, C., (1976) "Occupational Chemical Carcinogenesis: New Facts, Priorities and Perspectives," Int. Agency Res. Cancer, 3:127-149.

Manganaro, F. L., (1977) Director Env. Control and Energy Cons., Conrail, personal communication.

Marcoci, S. and Ionescu, M., (1974) ["The Toxic Action of Acrylonitrile on Fish,"] Strd. Prof. Calitatii Apelor, 16:7-22. (Rumanian).

Mascone, D., (1978) EPA/Emission Standards and Engineering Division, personal communication.

Matsumura, Y. and Arito, H., (1975) "Toxic Volatile Components of Organic Soil Consolidating Agents," Ind. Health, 13(3):135-149.

Mavrina, E. . and Il'ina, B. A., (1974) ["Change in Immunologic Reactivity of the Bodies of Students in a Technical Trade School During Practical Exercises Involving the Production of Nitrone,"] Gig. Sanit., 5:109-110. (Russian).

Mavrina, E. A. and Khromov, V. E., (1974) ["Functional Changes in the Body of Workers Engaged in Production of Nitron Fiber,"] Vrach. Delo., 6:129-131. (Russian).

McKee, J. W. and Wolf, H. W., (1963) "Water Quality Criteria," Resour. Agency of California State Water Resour. Control Board Publ. No. 3-A:127.

McLaughlin, M., Krivanek, N. D. and Trochimowicz, (1976) "Evaluation of Antidotes for Acrylonitrile Poisoning," Toxicol. Appl. Pharmacol., 37(1):133-134.

McOmie, W. A., (1949) "Comparative Toxicity of Methacrylonitrile and Acrylonitrile," J. Industr. Hyg. Toxicol., 31:113-116.

Mills, E. J., Jr. and Stack, V. T., Jr., (1955) "Acclimation of Microorganisms for the Oxidation of Pure Organic Chemicals," Proc. 9th Ind. Waste Conf., Purdue Univ., 449-464.

Milvy, P. and Wolff, M., (1977) "Mutagenic Studies with Acrylonitrile," Mutat. Res., 48:271-278.

Minami, M., Sato, U., Suzuki, A., Yamamura, K. and Ishizu, S., (1973) ["Acrylonitrile Poisoning. I. Result of Exposure to Acrylonitrile Vapor,"] Tokyo Joshi Ika Daigaku Zasshi, 43(10):849-855. (Japanese).

Monsanto Co., (1975) "Joint Toxic Action Between Acrylonitrile and Potassium Cyanide," Monsanto Co. Med. Dep., St. Louis.

Monsanto Co., (1976) "Monsanto 1976 Annual Report," St. Louis, Mo., pp. 14-30.

Monsanto Co., (1977a) "Acrylonitrile Sales Specifications," Monsanto Data Sheet, Monsanto Chem. Intermed. Co., St. Louis, Mo.

Monsanto Co., (1977b) In Response to OSHA's Request for Information on Acrylonitrile [42 FR 34327]. Letter to U.S. Dept. of Labor-OSHA, Docket Officer.

Morris, E. D., Jr. and Niki, H., (1971) "Reactivity of Hydroxyl Radicals with Olefins," J. of Phys. Chem., 75(23):3640-3641.

Morishita, T. and Mikami, J., (1975) ["Treatment of Waste Waters From Acrylonitrile Production Plants,"] Japan Kokai: Patent 75, 156, 263, 257-264. (Japanese).

MRI, (1977) "Sampling and Analysis of Selected Toxic Substances; Special Report Protocol for Sampling and Analysis for Acrylonitrile," Midwest Res. Inst., Kansas City, Missouri, prepared for EPA., 24 pp.

Murray, F. J., Nitschke, K. D., John, J. A., Smith, F. A., Quast, J. F., Blogg, C. D. and Schwetz, B. A., (1976) "Teratologic Evaluation of Acrylonitrile Monomer Given to Rats by Gavage," Toxicology Research Laboratory, Dow Chemical U.S.A., Midland, Mich., prepared for the Manufacturing Chemists Association.

Narasimhan, K. S., Shurpalekar, S. R. and Venkatesh, K. V. L., (1972) "Use of Fumigants in Prevention of Insect Infestation and Mould Growth in Papads," J. of Food Sci. and Technol., 9(3):134-137.

National Academy of Sciences, (1975) "Acrylonitrile" Assessing Potential Ocean Pollutants, A Rep. of the Study Panel on Assessing Potential Ocean Pollut. to the Ocean Affairs Board Comm. on Nat. Resour. Natl. Res. Counc., 209-227.

NIOSH, (1974) NIOSH Manual of Analytical Methods, P & CAM 127, NIOSH 75-121, U.S. Dept. of HEW, Cincinnati, Ohio *in* DuPont, (1977b), *op. cit.*

NIOSH, (1976) "NIOSH Analytical Methods for Set K," NTIS Rep. Number-PB-254 227.

NIOSH, (1977) "A Recommended Standard for Occupational Exposure to Acrylonitrile," DHEW (NIOSH) Publication No. 78-116, Cincinnati, Ohio, 14 pp.

Norris, J. M., (1977) "Status Report on the 2 Year Study Incorporating Acrylonitrile in the Drinking Water of Rats," Health Environmental Research, The Dow Chemical Company, Midland, Mich. (sponsored by the Manuf. Chem. Assoc.).

Norris, M. V., (1967) "Acrylonitrile," *Encycl. Indus. Chem. Analysis*, 4:368-381.

O'Berg, M. T., (1977) "Epidemiologic Study of Workers Exposed to Acrylonitrile - Preliminary Results," E. I. DuPont de Nemours & Co., Wilmington, Del.

Occupational Safety and Health Administration Act of 1970, PL 91-596, Approved December 29, 1970.

Ofengand, J., (1967) "The Function of Pseudouridylic Acid in Transfer Ribonucleic Acid. I. The Specific Cyanoethylation of Pseudouridine, Inosine, and 4-Thiouridine by Acrylonitrile," J. Biol. Chem., 242(21): 5034-5045.

OHM/SIRS, "Spill Data Information," E.P.A. Oil and Hazardous Materials Spill Information Retrieval System, Computerized Files.

OHM/TADS, "Technical Assistance Data System: Acrylonitrile [72T16574,"] E.P.A. Oil and Hazardous Materials Control Division, Computerized Files.

Olson, D. A., (1977) "Petrochemicals Outlook - 15: Acrylonitrile," Chem. Eng. Prog., November, 1977:42-45.

Orushev, T. and Popovski, P., (1973) ["Clinical Symptoms in Workers Occupationally Exposed to Acrylonitrile,"] God. Zb. Med. Fak. Skopje, 19:187-192. (Russian).

Ostrovskaya, R. S., Podrez, Z. G., Braginskaya, L. L., Boklag, E. P., Efremov, A. M. and Volkova, G. A., (1976) ["Health Status of Workers Currently Engaged in the Production of Acrylonitrile,"] Gig. Tr. Prof. Zabol., 6:8-12. (Russian).

Patterson, C., (1977) Kentucky Environmental Protection Bureau, Division of Hazardous Materials, personal communication.

Patterson, R. M., Bornstein, M. I., Garshick, E., (1976) "Assessment of Acrylonitrile as a Potential Air Pollution Problem, Volume VI," NTIS Rep. No.-PB-258-358.

Patty, F. A. (Ed.), (1963) "Acrylonitrile, CH_2:CHCN(Vinyl Cyanide, Propenenitrile)," *Industrial Hygiene and Toxicology*, 2nd Revised Edit., Vol. 2, 2009-2012.

Paulet, G., Desnos, J. and Battig, J., (1966) ["Toxicity of Acrylonitrile,"] Arch. Mal. Prof. Med. Trav., Secur. Soc., 27(12):849-856. (French).

Paulet, G. and Vidal, M., (1975) ["Toxicity of Some Acrylic and Methacrylic Esters of Acrylamide and Polyacrylamides,"] Arch. Mal. Prof. Med. Trav. Secur. Soc., 36(1-2):58-60. (French).

Ponder, T. C., (1976) "Propylene: Outlook Through 1985," Hydroc. Proc., Nov. 1976:213-215.

Portmann, J. E. and Wilson, K. W., (1971) "The Toxicity of 140 Substances to the Brown Shrimp and Other Marine Animals," Minist. of Agric., Fish. and Food, Fish. Lab., Burnham-on-Crouch, Essex, England; Shellfish Inf. Leafl., Number 22, 12 pp.

Prival, M. J., (1977), Written Testimony Before FDA in the Matter of AN Copolymers used to Fabricate Beverage Containers, Docket No. 76N-0070.

Pujado, P. R., Vora, B. V. and Krueding, A. P., (1977) "Newest Acrylonitrile Process." Hydrocarbon Process., May, 1977:169-172.

Quast, J. F., Enriquez, R. M., Wade, C. E., Humiston, C. G. and Schwetz, B. A., (1977) "Toxicity of Drinking Water Containing Acrylonitrile (AN) in Rats: Results after 12 Months," Toxicology Research Laboratory, Dow Chemical U.S.A., Midland, Mich., prepared for the Manufacturing Chemists Association.

Quast, J. F., Humiston, C. G., Schwetz, B. A., Frauson, L. A., Wade, C. E. and Norris, J. M., (1975) "A Six-Month Oral Toxicity Study Incorporating Acrylonitrile in the Drinking Water of Purebred Beagle Dogs," Toxicology Research Laboratory, Dow Chemical U.S.A., Midland, Mich., prepared for the Manufacturing Chemists Association.

Radimer, G. F., Davis, J. H. and Ackerman, A. B., (1974) "Fumigant-Induced Toxic Epidermal Necrolysis," Arch. Dermat., 110(1):103-104.

Renn, C. E., (1955) "Biological Properties and Behaviors of Cyanogenic Wastes," Sewage Ind. Wastes, 27(3):297-310.

Rogaczewska, T., (1975) ["Percutaneous Absorption of Acrylonitrile Vapors in Animals,"] Med. Pr., 26(6):459-465. (Polish).

Rogaczewska, T. and Piotrowski, J., (1968) ["Routes of Acrylonitrile Absorption in Man,"] Med. Pr., 19(4):349-354. (Polish).

Roudabush, R. L., Terhaar, C. J., Fassett, D. W. and Dziuba, S. P., (1965) "Comparative Acute Effects of Some Chemicals on the Skin of Rabbits and Guinea Pigs," Toxicol. Appl. Pharmacol., 7:559-565.

Rycroft, R. J. G., (1977) "Contact Dermatitis from Acrylic Compounds," Brit. J. Dermat., 96:685-687.

Sakurai, H. and Kusumoto, M., (1972) ["Epidemiologic Study of Health Impairment Among Acrylonitrile Workers,"] J. Sci. Labour (Tokyo), 48(5):273-282. (Japanese).

Sartorelli, E., (1966) ["Acute Acrilonitrile Intoxication,"] Med. Del Lav., 57(3):184-187. (Italian).

Scheufler, H., (1976) ["Experimental Testing of Chemical Agents for Embryotoxicity, Teratogenicity and Mutagenicity-Ontogenic Reactions of the Laboratory Mouse to These Injections and Their Evaluation - a Critical Analysis Method,"] Biol. Rundsch., 14(4):227-229. (German).

Schwartz, L., (1945) "Skin Hazards in the Manufacture and Processing of Synthetic Rubber," J. Am. Med. Assoc., 127(7):389-391.

Schwartz, W. A., Higgins, F. B., Jr., Lee, J. A., Newirth, R. and Perviev, J. W., (1975) "Engineering and Cost Study of Air Pollution Control for the Petrochemical Industry, Volume 2: Acrylonitrile Manufacture," Surv. Rep. on Atmos. Emiss. from the Petrochem. Ind. Ser. (EPA-450/3-73-006-b).

Seinfeld, J. H., (1975) Air Pollution: *Physical and Chemical Fundamentals*, McGraw-Hill, Inc., 159-217.

Seymour, R. B., (1975) "Chp. 13. Polynitriles, Polyacetals, and Polyalcohols," *Modern Plastics Technology*, Prentice-Hall, Reston, Va., 231-233.

Shustov, V. J., (1968) ["Clinical Manifestations and Hematological Changes in Workers Employed in the Production of Acrylonitrile at the Saratov Chemical Combine,"] Gig. Tr. Prof. Zabol., 7:25-29. (Russian).

Shustov, V. Y. and Mavrina, E. A., (1975) ["Clinical Picture of Chronic Poisoning in the Production of Nitrone,"] Gig. Tr. Prof. Zabol., 3:27-29. (Russian).

Slater, E. E., Anderson, M. D. and Rosenkranz, S., (1971) "Rapid Detection of Mutagens and Carcinogens," Cancer Res., 31(7):970-973.

Smyth, H. F. and Carpenter, C. P., (1948) "Further Experience with the Range Finding Test in the Industrial Toxicology Laboratory," J. Industr. Hyg. Toxicol., 30:63-68.

Smyth, H. F., Weil, C. S., Jean, S., Carpenter, C. P., (1969) "Exploration of Joint Toxic Action: Twenty-seven Industrial Chemicals Intubated in Rats in All Possible Pairs," Toxicol. Appl. Pharmacol., 14(2):340-347.

Solid Waste Disposal Act, PL 93-14, Approved April 9, 1973.

Solovei, L. I., (1974) ["Change in Protein Metabolism Indexes in the Liver and Serum in Rats After Poisoning with Acrylonitrile,"] Narusheniya Metab., Tr. Nauchn. Konf. Med. Inst. Zapadn. Sib., 1st:109-112. (Russian).

Spassovski, M., (1976) "Health Hazards in the Production and Processing of Some Fibers, Resins, and Plastics in Bulgaria," Environ. Health Perspect., 17:199-202.

Squire, R. A., (1978) Prepared Statement for OSHA Public Hearing on Proposed Standard for Occupational Exposure to Acrylonitrile, March 21, 1978; exhibit #28.

SRI, (1975 and 1977) Directory of Chemical Producers -U.S.A. Stanford Research Institute, Menlo Park, Calif.

SRI, (1976) "Interim Report: *In Vitro* Microbiological Mutagenicity Studies of Dow Chemical Company Compounds," Stanford Research Institute Project No. LSC-4378, prepared for the Dow Chemical Company.

Standard Oil Co., (1976) Stand. Oil Co. Annual Report 1976, 16-18.

Standard Oil Co., (1977) In Response to OSHA's Request for Information on Acrylonitrile, [42 FR 33043] Letter to U.S. Dept. of Labor - OSHA, Docket Officer

Standish, N. W., (1974) "Compositions Fertilizing and Treating Soil Containing Nematocides," U.S. Pat. 3,801,300.

Steichen, R. J., (1976) "Modified Solution Approach for the Gas Chromatographic Determination of Residual Monomers by Head-Space Analysis," Anal. Chem., 48(9):1398-1402.

Stobaugh, R. B., Clark, G. McH. and Camirand, G. D., (1971) "Acrylonitrile: How, Where, Who - Future," Hydrocarbon Process., 50(1): 109-120.

Svirbely, J. L. and Floyd, E. P., (1961) "Toxicologic Studies of Acrylonitrile, Adiponitrile, and B,B'-Oxydipropionitrile III. Chronic Studies," Meeting paper, AINA-ACSIH, Detroit, Michigan.

Szabo, S., Bailey, K. A., Boor, P. J. and Jaeger, R. J., (1977) "Acrylonitrile and Tissue Glutathione: Differential Effect of Acute and Chronic Interactions," Biochem. Biophys. Res. Comm., 79:32-37.

Szabo, S., Reynolds, E. S., Komanicky, P., Moslen, M. T. and Melby, J. C., (1976) "Effect of Chronic Acrylonitrile Ingestion on Rat Adrenal," Toxicol. Appl. Pharmacol., 37(1):133.

Szabo, S. and Selye, H., (1971) "Adrenal Apoplexy and Necrosis Produced by Acrylonitrile," Endokrinologie, 57(3):405-408.

Tada, O., (1971) "Methods for Determinations of Toxic Substances in Air-Organic Compounds," J. of Sci. of Labour, (Part II) 47(12):789-796.

Tarkowski, S., (1968) ["Effect of Acrylonitrile on Certain Properties of Cytochrome Oxidase,"] Med. Pr., 19(6):525-531. (Polish).

Texaco Inc., (1977) In Response to OSHA's Request for Information on Occupational Exposure to Acrylonitrile, [42 FR 33043] Unpubl. Letter to U.S. Dep. of Labor-OSHA, Docket Officer.

Townsend, P., (1974) "Acrylonitrile-Markets, Technology, and Economics," Applied Polymer Symposium 25: Acrylonitrile in Macromolecules, John Wiley and Sons, Inc., 1-18.

Tsuchiya, Y. and Sumi, K., (1977) "Thermal Decomposition Products of Polyacrylonitrile," J. of Appl. Polym. Sci., 21(4):975-980.

Tullar, P. E., (1947) "Final Report on the Pharmacology and Toxicology of Acrylonitrile and Acrylon," Kalusowski Memorial Research Laboratories, George Washington University.

Union Carbide Corp., (1977) In Response to OSHA's Request for Information on Occupational Exposure to Acrylonitrile, [42 FR:33043] Unpubl. Letter to U.S. Dep. of Labor-OSHA, Docket Officer.

Uniroyal, Inc., (1977) In Response to OSHA's Request for Information on Acrylonitrile, [42 FR:33043] Unpubl. Letter to U.S. Dep. of Labor-OSHA, Docket Officer.

U.S. Bureau of the Census, (1965-1976a) "U.S. Imports for Consumption and General Imports," Report FT 246.

U.S. Bureau of the Census, (1972-1976b) "U.S. Exports/Domestic Merchandise, SIC-Based Products by World Areas," Report FT 610.

U.S. Int. Trade Comm., (1973-1976) "Synthetic Organic Chemicals U.S. Production and Sales, 1976," U.S. Int. Trade Comm. Publ. 833.

U.S. Tariff Comm., (1966-1972) "Synthetic Organic Chemicals" Tariff. Comm. Publ. 248.

Vainio, H. and Mäkinen, A. (1977) "Styrene and Acrylonitrile Induced Depression of Hepatic Nonprotein Sulfhydryl Content in Various Rodent Species," Res. Commun. Chem. Pathol. Pharmacol., 17(1):115-124.

Vistron, (1978) letter from D. W. Hollingsed of Vistron to F. Letkiewicz of OTS/EPA dated 5/3/78; personal communication D. W. Hollingsed and P. Hilgard of OTS/EPA on 5/10/78.

Venitt, S., Bushell, C. T. and Osborne, M., (1977) "Mutagenicity of Acrylonitrile (Cyanoethylene) in *Escherichia coli*," Mutat. Res., 45:283-288.

WHO, (1965) "Evaluation of the Hazards to Consumers Resulting from the Use of Fumigants in the Protection of Food," Food and Agriculture Meeting Report No. PL/1965/10, WHO/Food Add./28.65, 14-18.

Wilcox, W. S. and Goldstein, J. H., (1954) "The Microwave Spectrum of Vinyl Cyanide," J. of Chem. Phys., 22(3):516-518.

Wilson, R. H., (1944) "Health Hazards Encountered in the Manufacture of Synthetic Rubber," J. Am. Med. Assoc., 124(11):701-703.

Wilson, R. H., Hough, G. V. and McCormick, W. E., (1948) "Medical Problems Encountered in the Manufacture of American-Made Rubber," Indus. Med., 17(6):199-207.

Wilson, R. H. and McCormick, W. E., (1949) "Acrylonitrile - Its Physiology and Toxicology," Indus. Med. and Surg., 18:223-245.

Wisniewska-Knypl, J. M., Knobloch, K., Jablonska, J. and Ruta, U., (1970) ["Decrease of Tissue Respiration, Activity of Oxoglutarate Dehydrogenase and Level of Sulfhydryl Groups in Acute Acrylonitrile Intoxication in Rats,"] Med. Pr., 21(6):543-549. (Polish).

Wright, P. L., (1977) "Studies on the Metabolism of Acrylonitrile," Testimony before FDA *in* Monsanto Co. (1976b) *op. cit.*, Appendix A: A-20 to A-28.

Yoshikawa, H., (1968) ["Toxicity of Nitrile Compounds. 1. Aliphatic nitriles,"] Med. and Biol., 77(1):1-4. (Japanese).

Young, J. D., Slauter, R. W. and Karbowski, R. J., (1977) "The Pharmacokinetic and Metabolic Profile of ^{14}C-Acrylonitrile Given to Rats by Three Routes," Toxicology Research Lab. Dow Chemical U.S.A., Midland, Mich., prepared for the Manufacturing Chemists Association.

Zeller, H., Hoffman, H. T., Thiess, A. M. and Hey, W., (1969) ["Toxicity of Nitriles: Results of Animal Experiments and Industrial Experiences During 15 Years,"] Zentralbl. Arbeitsmed. Arbeitsschultz, 19(8):225-238. (German).

Zotova, L. V., (1975) ["Working Conditions in the Production of Acrylonitrile and Their Effect on Workers,"] Gig. Tr. Prof. Zabol., 8:8-11. (Russian).

CONCLUSIONS AND RECOMMENDATIONS

Limited data on environmental fate and the absence of monitoring data make it difficult to assess the effects of environmental contamination by acrylonitrile at the present time. However, potential contamination is possible during production, transport, end-use and waste-handling. With the projected growth of acrylonitrile markets, concomitant increases in potential hazards can be expected. The need for additional environmental evaluation studies of acrylonitrile is apparent. Studies sponsored by the EPA for AN are currently underway at and near production sites. Research on the biodegradability of acrylonitrile is ongoing at several universities, e.g., University of Texas and Rutgers University. Additional research, however, on chemical breakdown (particularly in the atmosphere), transport and persistence of AN in the environment would be desirable. Presently it can only be speculated, based on physical-chemical properties and very limited data, that small quantities of acrylonitrile will not persist or bioconcentrate.

The effects of large acrylonitrile spills on ecosystems have not been investigated. Controlled studies and intensive monitoring of actual spills would be desirable.

The toxic effects of acrylonitrile to mammals are well known, particularly for acute exposures. Ongoing studies sponsored by the Manufacturing Chemists Association will contribute to long-term assessment of toxic and carcinogenic effects in rats. There is a paucity of data of effects on terrestrial microorganisms and plants. Without such information the effects of acrylonitrile on ecosystems cannot be fully known.

As more data emerge, assessment of the environmental exposure to acrylonitrile will become more precise. Implementation of pending regulations should reduce levels of acrylonitrile in some environmental media.

Appendix A

Summary of Sources Employed

References used in this report were selected from searches of automated information retrieval systems, indices, standard reference works, journals, books, etc. Manufacturers, researchers, and federal and state agencies, among others, were contacted directly.

The following is a list of on-line systems searched:

- Cancerline
- Chemical Abstracts Condensates
- Chemical Industry Notes
- Economic Information System
- Enviroline
- Federal Index
- Federal Index Weekly
- Food Science and Technology Abstracts
- Marketing Abstracts
- Marketing Abstracts Weekly
- National Technical Information System
- Office of Hazardous Materials Technical Assistance Data System
- Pollution Abstracts
- Smithsonian Science Information Exchange
- Science Citation Index
- Toxline
- Toxback
- Water Resources Abstracts

Also the Technical Information Center data base was searched by the National Institute of Occupational Safety and Health.

Manually searched indices included:

- Biological Abstracts (1959-1977)
- Chemical Abstracts (1957-1971)
- Excerpta Medica
  - Cancer (1953-1977)
  - Pharmacology and Toxicology (1965-1977)
  - Developmental Biology and Teratology (1965-1976)
  - Environmental Health and Pollution Control (1972-1976)
  - Occupational Health and Industrial Medicine (1971-1976)
- Index Medicus (1957-1977).

Appropriate books and compendia were examined. In addition, current journals were screened. The literature search is considered complete through April 1978.